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Publication numb r: **0 533 240 A2**

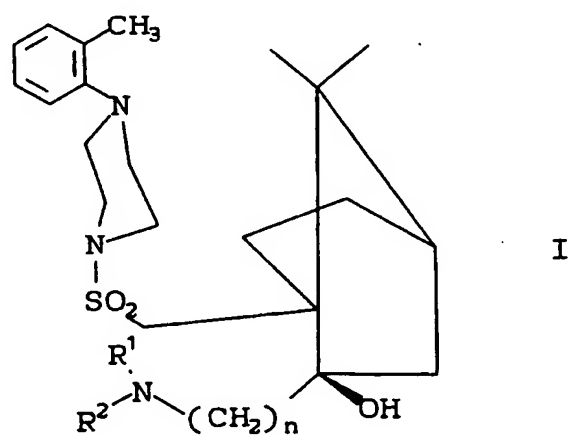
**EUROPEAN PATENT APPLICATION**

- (21) Application number: 92202720.6
- (22) Date of filing: 08.09.92
- (51) Int. Cl.<sup>5</sup>: **C07D 295/22, C07D 207/26, C07D 233/54, C07D 453/02, C07D 303/34, C07D 211/60, C07D 211/62, C07D 213/38, A61K 31/495**

- (30) Priority: 16.09.91 US 760271
- (43) Date of publication of application: 24.03.93 Bulletin 93/12
- (84) Designated Contracting States: CH DE FR GB IT LI NL
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- (54) **Substituted amine derivatives of piperazinylcamporsulfonyl oxytocin antagonists.**
- (57) **Compounds of the formula:**



**EP 0 533 240 A2**

The compounds of formula I are oxytocin antagonists useful in the treatment of pr term labor, dysm norrhea and for the stoppage of labor pr paratory to cesar an delivery. Also disclosed are pharmaceutical compositions containing these compounds, methods of their use and methods of their preparation.

FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents in obstetric and gynecologic therapy. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, stopping labor preparatory to Cesarean delivery, and in the treatment of dysmenorrhea. At the present time, there is a need in the area of obstetric and gynecologic therapy for such agents.

10 BACKGROUND OF THE INVENTION

In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus in utero is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include  $\beta_2$ -adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading  $\beta_2$ -adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other  $\beta_2$ -adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin is the physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

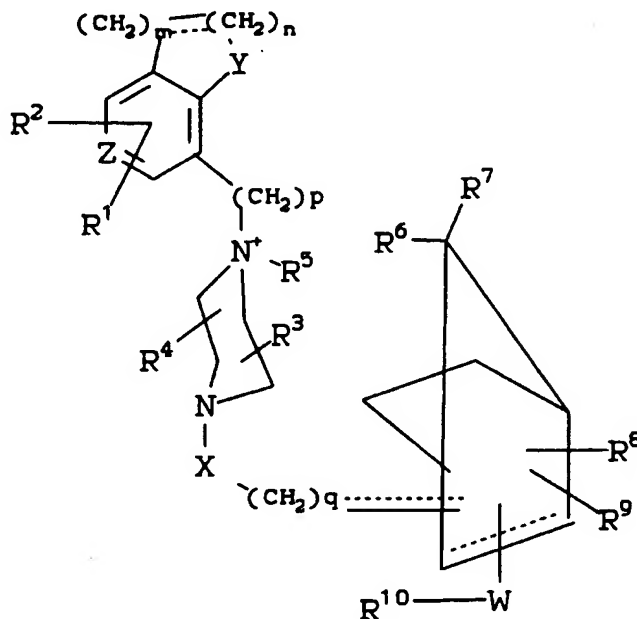
The compounds of the present invention can also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

It has now been found that compounds of formula I are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparation to Cesarean delivery.

SUMMARY OF THE INVENTION

The compounds of the present invention are those of the general structural formula:



and the pharmaceutically acceptable salts thereof, wherein

W is

an optional substituent that, when present, is substituted or unsubstituted alkyl where said substituent is carboxyl;

X is

- (1) carbonyl or
- (2) sulfonyl;

Y is

- (1) hydrogen,
- (2) alkyl or
- (3) NH;

Z is

- (1) C or
- (2) N;

R<sup>1</sup> and R<sup>2</sup> are independently

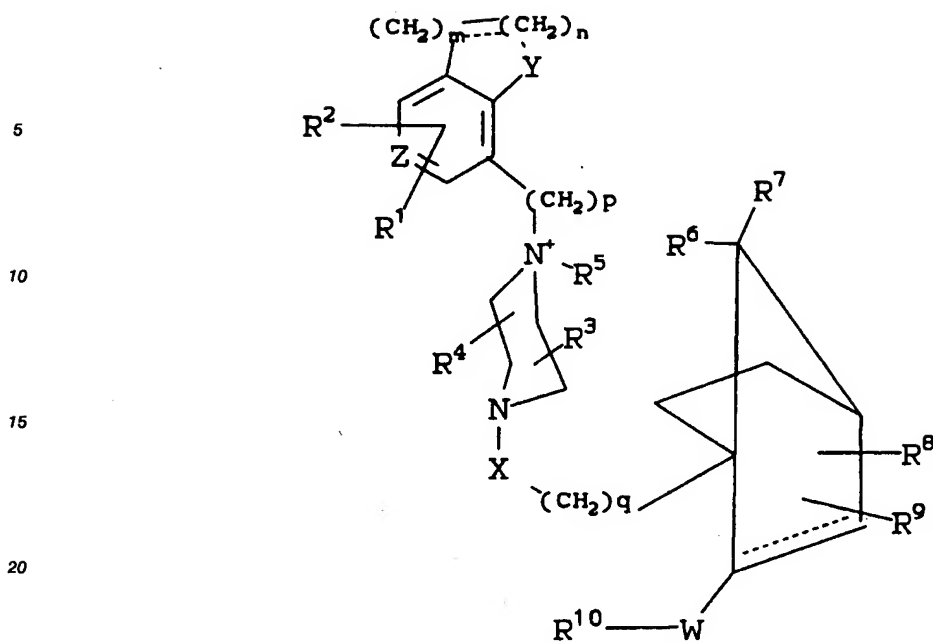
- (1) hydrogen,
- (2) halogen,
- (3) alkoxy,
- (4) alkylsulfonyl or
- (5) unsubstituted or substituted alkyl wherein said substituent is; amino, alkylamino, or dialkylamino;

R<sup>3</sup> and R<sup>4</sup> are independently

- (1) hydrogen,
- (2) alkyl,
- (3) substituted alkyl where said substituents is amino, alkylsulfonyl, arylsulfonyl, alkylamino, or

- 5  $R^5$  is
- dialkylamino;
  - (4) phenylalkyl or
  - (5) oxo;
- 10  $R^6$  and  $R^7$  are independently
- (1) hydrogen,
  - (2) alkyl or
  - (3) joined to form unsubstituted or substituted cycloalkyl where said substituent is
  - hydroxy or
  - hydroxyalkyl;
- 15  $R^8$  and  $R^9$  are independently
- (1) hydrogen,
  - (2) hydroxy,
  - (3) oxo
  - (4) halogen,
  - (5) oxime,
  - (6) cyclic epoxide,
  - (7) methylene,
  - (8) carboxyl,
  - (9) alkoxycarbonyl,
  - (10) alkylcarbonyloxy,
  - (11) alkoxycarbonylalkoxy,
  - (12) sulfonyloxy,
  - (13) trihaloalkylsulfonyloxy,
  - (14) unsubstituted or substituted amino where said substituent is
  - alkyl,
  - carboxylalkyl or
  - alkoxycarbonylalkyl; and
- 20  $R^{10}$  is
- 25 substituted alkyl where said substituent is  $-N(R^{11})(R^{12})$ , where  $R^{11}$  is defined as
- hydrogen or
  - alkyl; and
- 30  $R^{12}$  is defined as
- hydrogen
  - alkylcarbonyl or
  - substituted or unsubstituted alkyl where said substituent is
  - (1) hydroxy,
  - (2) alkoxy,
  - (3) carboxy
  - (4) sulfonyl,
  - (5) alkylsulfonyl,
  - (6) carbonyl,
  - (7) alkylcarbonyl,
  - (8) alkoxycarbonyl,
  - (9) phenyl or
  - (10) unsubstituted 5 or 6-membered unsaturated heterocyclic rings
  - having 1 or 2 heteroatoms wherein said heteroatom is N; and
  - m, n, p and q are integers from 0 to 2

More particularly preferred compounds are those of the general structural Formula:



and the pharmaceutically acceptable salts thereof, wherein W is an optional substituent that, when present, substituted or unsubstituted alkyl where said substituent is carboxyl;

X is

- (1) carbonyl or  
(2) sulfonyl;

Y is

- (1) hydrogen,  
(2) alkyl or  
(3) NH;

Z is

- (1) C or  
(2) N;

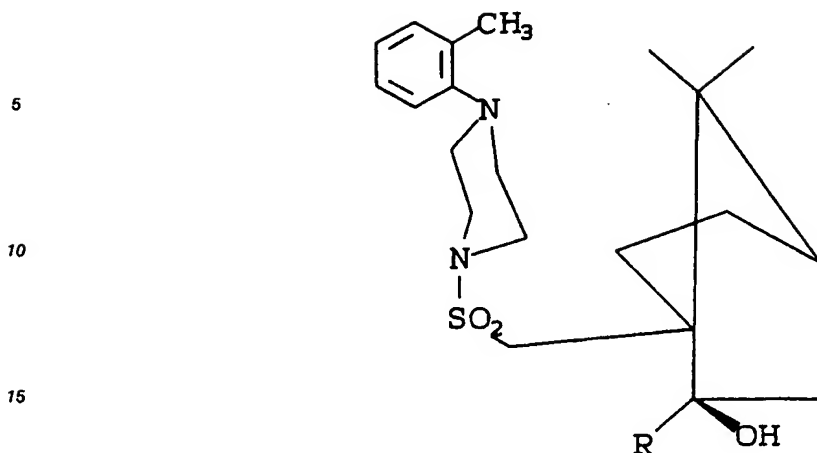
R<sup>1</sup> and R<sup>2</sup> are independently

- (1) hydrogen,  
(2) halogen,  
(3) alkoxy,  
(4) alkylsulfonyl or  
(5) unsubstituted or substituted alkyl wherein said substituent is;  
amino,  
alkylamino, or  
dialkylamino;

R<sup>3</sup> and R<sup>4</sup> are independently

- (1) hydrogen,  
(2) alkyl,  
(3) substituted alkyl where said substituent is  
amino,  
alkylsulfonyl,  
arylsulfonyl,  
alkylamino, or  
dialkylamino;  
(4) phenylalkyl or

- (5) oxo;
- R<sup>5</sup> is
- (1) hydrogen or
- (2) oxo
- R<sup>6</sup> and R<sup>7</sup> are independently
- (1) hydrogen,
- (2) alkyl or
- (3) joined to form unsubstituted or substituted cycloalkyl where said substituent is
- hydroxy or
- hydroxyalkyl;
- R<sup>8</sup> and R<sup>9</sup> are independently
- (1) hydrogen,
- (2) hydroxy,
- (3) oxo
- (4) halogen,
- (5) oxime,
- (6) cyclic epoxide,
- (7) methylene,
- (8) carboxyl,
- (9) alkoxycarbonyl,
- (10) alkylcarbonyloxy,
- (11) alkoxycarbonylalkoxy,
- (12) sulfonyloxy,
- (13) trihaloalkylsulfonyloxy,
- (14) unsubstituted or substituted amino where said substituent is
- alkyl,
- carboxyalkyl, or
- alkoxycarbonylalkyl;
- R<sup>10</sup> is
- unsubstituted or substituted alkyl where said substituent is
- N(R<sup>11</sup>)(R<sup>12</sup>), where R<sup>11</sup> is defined as
- hydrogen or
- alkyl, and
- R<sup>12</sup> is defined as
- hydrogen,
- alkylcarbonyl or
- substituted or unsubstituted alkyl where said substituent is
- (1) hydroxy,
- (2) alkoxy,
- (3) carboxy,
- (4) sulfonyl,
- (5) alkylsulfonyl,
- (6) carbonyl,
- (7) alkylcarbonyl,
- (8) alkoxycarbonyl,
- (9) phenyl or
- (10) unsubstituted 5 or 6-membered unsaturated heterocyclic rings having 1 or 2 heteroatoms wherein said heteroatom is N; and
- m, n, p, and q are integers from 0 to 2.
- Most preferred are those compounds of the general formula:



20 and the pharmaceutically acceptable salts thereof, wherein

R is

substituted alkyl where said substituted is -N(R<sup>1</sup>)(R<sup>2</sup>), where R<sup>1</sup> is defined as  
hydrogen or  
alkyl, and

25 R<sup>2</sup> is defined as

hydrogen,  
alkylcarbonyl or  
substituted or unsubstituted alkyl where said substituent is

(1) hydroxyl,

(2) alkoxy

(3) carboxy,

(4) alkylsulfonyl,

(5) alkylcarbonyl

(6) alkoxy carbonyl,

(7) aralkoxy carbonyl,

(8) phenyl or

(9) unsubstituted 5 or 6-membered unsaturated heterocyclic rings having 1 or 2  
heteroatoms wherein said heteroatom is N.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the  
40 compounds of this invention which are generally prepared by reacting the free base with a suitable organic  
or inorganic acid. Representative salts include the following salts:

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5	Acetate Benz n sulfonate B nzoate Bicarbonate Bisulfate Bitartrate Borate Bromide Calcium Edetate Camsylate Carbonate Chloride	Lactobionate Laurate Malate Maleate Mandelate Mesylate Methylbromide Methylnitrate Methylsulfate Mucate Napsylate Nitrate
10	Clavulanate Citrate	N-methylglucamine ammonium salt
15	Dihydrochloride Edetate Edisylate Edisylate Estolate	Oleate Oxalate Pamoate (Embonate) Palmitate Pantothenate Phosphate/diphosphate Polygalacturonate
20	Esylate Fumarate Gluceptate Gluconate Glutamate Glycolylarsanilate Hexylresorcinat	Salicylate Stearate Subacetate Succinate Tannate Tartrate
25	Hydrabamine Hydrobromide Hydrochloride Hydroxynaphthoate Iodide Isethionate Lactate	Teoclote Tosylate Triethiodide Valerate
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35		

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes, alkenes and alkynes with one or more degrees of unsaturation at any position on the chain, of one to ten total carbon atoms or any number within this range.

The term "aryl" shall mean phenyl, naphthyl and fluorenyl.

The term "cycloalkyl" shall mean cyclic rings of alkanes, alkenes or alkynes with one or more degrees of unsaturation at any position of the ring, of three to eight total carbon atoms.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. aralkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Designated numbers of carbon atoms (e.g. C<sub>1-10</sub>) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

Where multiple substituent moieties are disclosed or claimed, the substituted compounds can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The term "oxo" shall refer to the substituent =O.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th



week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "cesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

5 The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent.

The ability of the compounds of formula I to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and especially  
10 dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

Because of the known relationship of vasopressin to oxytocin, the compounds of the present invention are also useful as vasopressin antagonists. Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders, including their use as diuretics and their use in  
15 congestive heart failure.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those  
20 of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and  
25 the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.3-6.0 gm/day orally. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute  
30 during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of  
35 a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended  
40 form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and  
45 coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl  
50 cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

55 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspar-

5 tamidephenol, or poly thylen oxidepolylysine substitut d with palmitoyl residues. Furthermore, the compounds of th pr sent inv ntion may be coupled to a class of biodegradable polym rs us ful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

10 The compounds of formula I can be prepared readily according to the following reaction Schemes (in which all variables are as defined before) and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

15 The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

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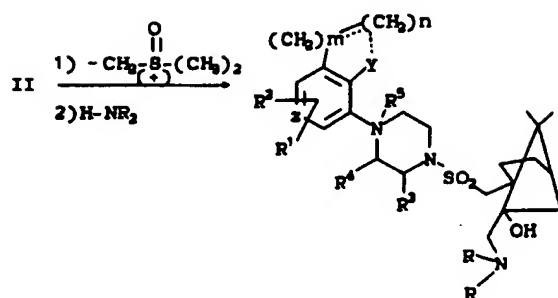
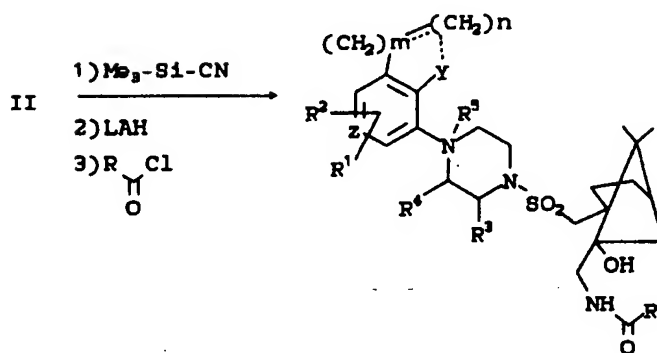
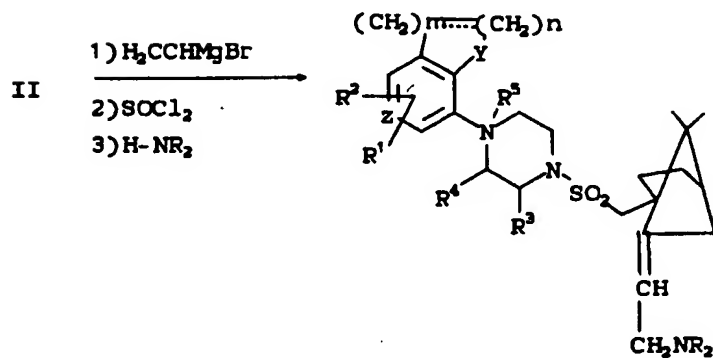
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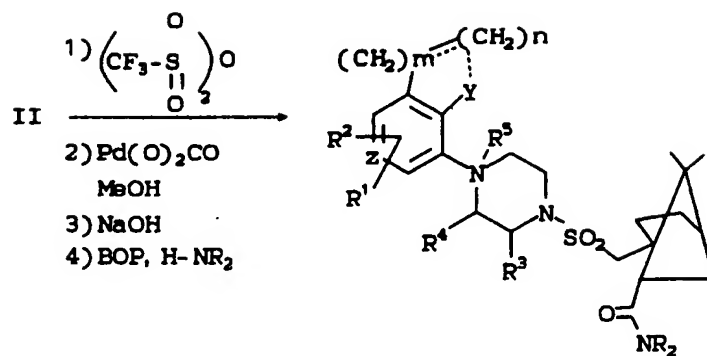
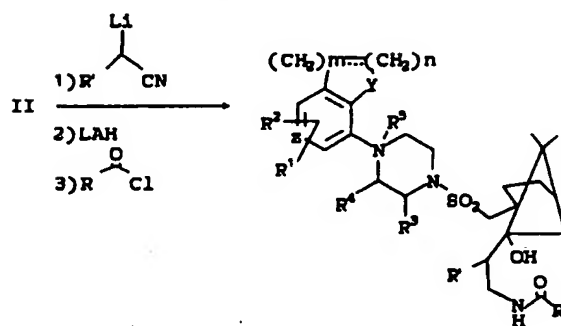
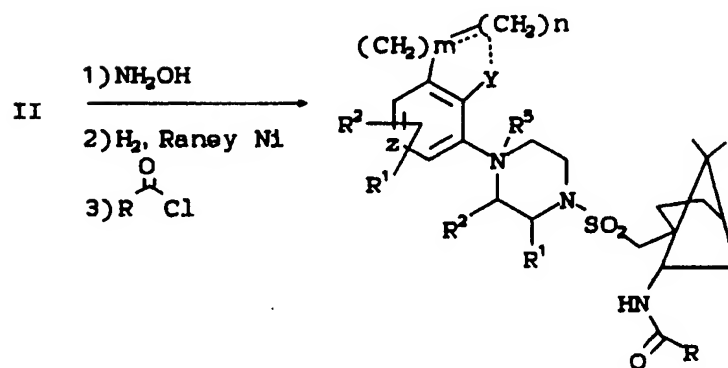
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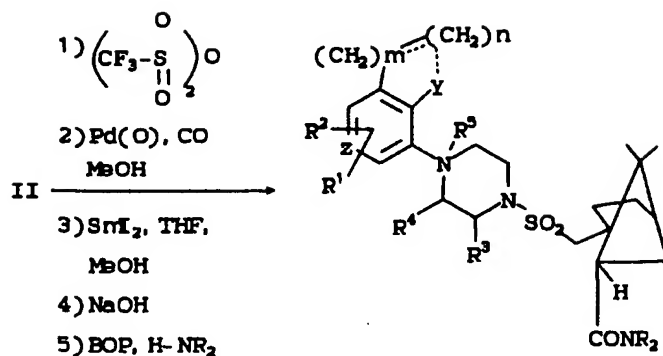
Where W is a suitable  
leaving group



SCHEME 2SCHEME 3SCHEME 4

SCHEME 5SCHEME 6SCHEME 7

## SCHEME 8



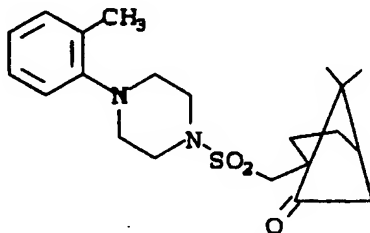
Abbreviations used in the Examples are as follows:

TEA	= triethylamine
DIEA	= diisopropylethylamine
BOP	= benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate
THF	= tetrahydrofuran
DMF	= dimethylformamide
LAH	= lithium aluminum hydride
TFA	= trifluoroacetic acid
HPLC Method A	= 15 min. linear gradient 95:5 A:B to 0:100 A:B A = $\text{H}_2\text{O}$ containing 0.1% by vol. TFA B = $\text{CH}_3\text{CN}$ containing 0.1% by vol. TFA 2.0 mL/min flow rate 12 cm $\text{C}_{18}$ reverse phase column UV detection (215 nm)

TLC was performed on 20 cm plates coated with silica gel (250 microns) from Analtech.

## Example 1

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)-PIPERAZINE



To a stirred,  $0^\circ\text{C}$  solution of 1-(o-tolyl)piperazine hydrochlorid (50.0 g; 235 mmol) and TEA (83 mL; 590 mmol) in chloroform (1000 mL) was added (+)-10-camporsulfonyl chloride (65.5 g; 260 mmol). The solution was stirred at  $0^\circ\text{C}$  for 1 h and then at ambient temperature for 3 h. The solution was extracted with 5% aqueous HCl (2 x 500 mL), water (500 mL), and saturated aqueous  $\text{NaHCO}_3$  (2 x 500 mL). The organic phase was dried ( $\text{MgSO}_4$ ), filtered, and the solvent was removed under reduced pressure. The resulting solid was recrystallized from methanol to give the title compound, mp  $112-114^\circ\text{C}$  (69 g; 75%).

Anal: (C <sub>21</sub> H <sub>30</sub> N <sub>2</sub> O <sub>3</sub> S)			
Calc.	C, 64.57;	H, 7.74;	N, 7.17
Found	C, 64.52;	H, 7.68;	N, 6.99

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TLC: R<sub>f</sub> 0.49 (75:25 hexane/ethyl acetate)

HPLC (method A): retention time 10.33 min

FAB MS: m/z 391 (M<sup>+</sup> + H)

10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.2 (m, 2H), 7.0 (m, 2H), 3.45 (m, 4H), 3.40 (d, J = 16 Hz, 1H), 3.0 (m, 4H), 2.57 (m, 1H), 2.40 (dt, J<sub>d</sub> = 14 Hz, J<sub>t</sub> = 3 Hz, 1H), 2.30 (s, 3H), 2.10 (m, 2H), 1.96 (d, J = 14 Hz, 1H), 1.67 (m, 1H), 1.44 (m, 1H), 1.18 (s, 3H), 0.91 (s, 3H)

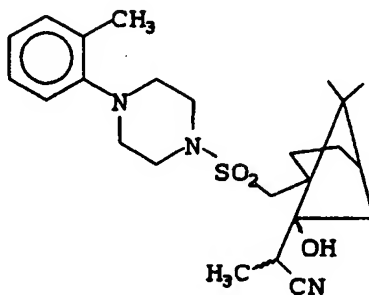
Example 2

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1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-(1-CYANO)ETHYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYL PHENYL)PIPERAZINE:

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To a stirred, -78°C solution of diisopropylamine (21.0 mL; 150 mmol) in THF (350 mL) was added n-butyllithium (60 mL of a 2.5 M solution in hexane; 150 mmol). The solution was warmed to 0°C for 15 min, then cooled to -78°C. A solution of propionitrile (10.1 mL; 141 mmol) in THF (75 mL) was added dropwise, and the resulting solution was stirred at -78°C for 45 min. A -78°C solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (50.0 g; 128 mmol) in THF (350 mL) was added via cannula, and the resulting solution was stirred at -78°C for 5 min. A solution of 5:1 THF/water (100 mL) was added and the mixture was warmed to ambient temperature. The mixture was diluted with EtOAc (500 mL) and washed with 5% aqueous citric acid (2 x 500 mL), and brine (250 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvents were removed under reduced pressure to give a foam. The major isomer by TLC was obtained by crystallization from ether, mp 163-165°C

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Anal: (C <sub>24</sub> H <sub>35</sub> N <sub>3</sub> O <sub>3</sub> S)			
Calc.	C, 64.69;	H, 7.92;	N, 9.43
Found	C, 64.72;	H, 7.99;	N, 9.35

TLC: R<sub>f</sub> 0.31 (75:25 hexane/ethyl acetate)

HPLC (method A): retention time 10.20 min

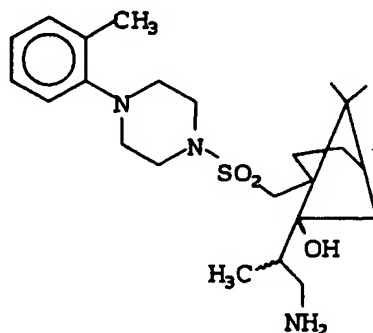
FAB MS: m/z 446 (M<sup>+</sup> + H)

50 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 2H), 3.70 (d, J = 15 Hz, 1H), 3.68 (s, 1H), 3.49 (m, 4H), 3.38 (d, J = 15 Hz, 1H), 2.75 (q, J = 7 Hz, 1H), 2.30 (s, 2H), 2.05 (m, 2H), 1.7-1.9 (m, 3H), 1.47 (d, J = 7 Hz, 3H), 1.41 (d, J = 12 Hz, 1H), 1.40 (s, 3H), 1.15 (s, 3H), 1.04 (m, 1H)

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## Example 3

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred,  $-78^{\circ}\text{C}$  solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-(1-cyano)ethyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (25.0 g; 56.2 mmol) in THF (350 mL) was added dropwise a 1.0 M solution of LAH in THF (170 mL; 170 mmol). The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 1 h, and then warmed to  $0^{\circ}\text{C}$  for 3 h. Ether (300 mL) was added, followed by the slow dropwise addition of 5 M NaOH solution (35 mL). The resulting suspension was warmed to ambient temperature and stirred for 1 h. EtOAc (250 mL) was added and stirring was continued for 30 min. The solids were removed by filtration through Celite and washed with EtOAc. The filtrate solvents were removed under reduced pressure to give a foam. The title compound was obtained by crystallization from methanol, mp  $172-174^{\circ}\text{C}$  (17.2 g; 68%).

Anal: ( $\text{C}_{24}\text{H}_{39}\text{N}_3\text{O}_3\text{S}$ )

Calc.	C, 64.11;	H, 8.74;	N, 9.35
Found	C, 64.09;	H, 8.88;	N, 9.31

TLC:  $R_f$  0.50 (95:5:0.5  $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ )

HPLC (method A): retention time 9.80 min

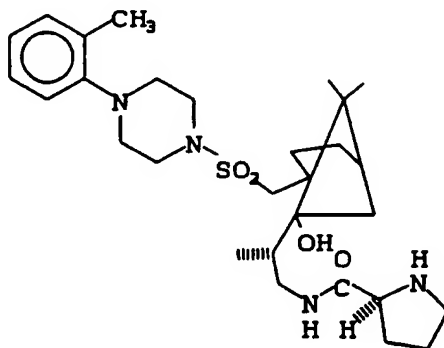
FAB MS:  $m/z$  450 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.20 (m, 2H), 7.05 (m, 2H), 2.32 (s, 3H), 1.13 (d,  $J=6$  Hz, 3H), 1.11 (s, 3H), 1.02 (s, 3H)



## Example 4

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (2.00 g; 4.45 mmol) in DMF (30 mL) was added N<sup>ε</sup>-Fmoc-L-proline (1.58 g; 4.68 mmol), BOP (2.17 g; 4.90 mmol), and DIEA (1.71 mL; 9.80 mmol). After 16 h, diethylamine (6 mL) was added and the solution was stirred at ambient temperature for 3 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>29</sub> H <sub>46</sub> N <sub>4</sub> O <sub>4</sub> S)			
Calc.	C, 52.48;	H, 6.50;	N, 7.56
Found	C, 52.46;	H, 6.50;	N, 7.69

1.7 TFA, 0.05 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.45 (90:10:1 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

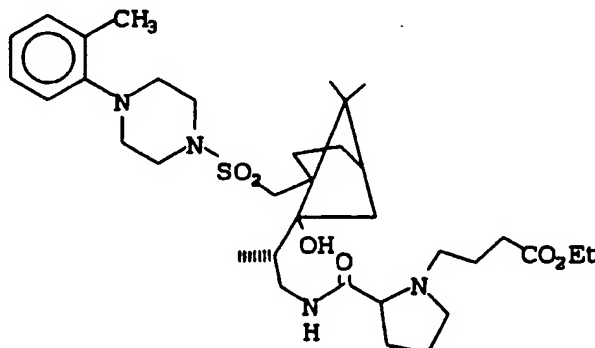
HPLC (method A): retention time 8.60 min

FAB MS: m/z 547 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.55 (br t, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.31 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.99 (d, J = 7 Hz, 3H)

## Example 5

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(ETHOXYCARBONYLPROPYL)PROLYL)AMINO)-PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE:



# EP 0 533 240 A2

To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; MW=679; 2.21 mmol) in DMF (15 mL) was added ethyl 4-bromobutyrate (538 mg; 2.76 mmol), and DIEA (1.15 mL; 6.63 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: (C <sub>35</sub> H <sub>55</sub> N <sub>4</sub> O <sub>6</sub> S)			
Calc.	C, 51.99;	H, 6.48;	N, 6.17
Found	C, 52.01;	H, 6.33;	N, 6.17

2.1 TFA, 0.1 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.40 (95:5 CHCl<sub>3</sub>:MeOH)

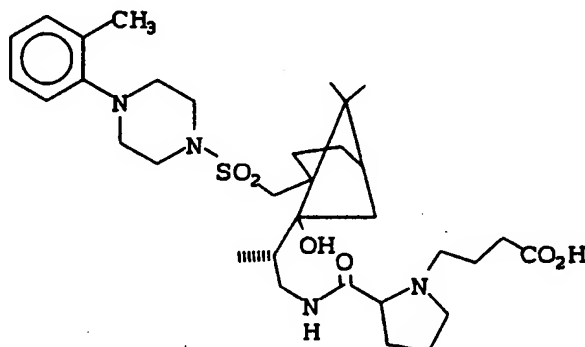
HPLC (method A): retention time 10.23 min

FAB MS: m/z 661 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.55 (m, 1H), 7.20 (m, 2H), 7.08 (m, 2H), 2.35 (s, 3H), 1.25 (t, J=6Hz, 3H), 1.14 (s, 3H), 1.03 (overlapping s and d, 6H)

## Example 6

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(3-CARBOXYPROPYL)PROLYL)AMINO)PROPYL-BICYCLO(2.2.1) HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-N-(ethoxycarbonylpropyl)prolyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.00 g; MW=909; 1.10 mmol) in THF (15 mL) was added 1 M NaOH solution (1.0 mL; 4.0 mmol) until a pH 10 solution persisted for 1 h. The solution was acidified to pH 7 by addition of citric acid and the solvents were removed under reduced pressure. The residue was dissolved in dichloromethane (75 mL) and washed with water (3 x 25 mL), dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was lyophilized from dioxane-water to give the title compound as a white powder.

Anal: (C <sub>33</sub> H <sub>52</sub> N <sub>4</sub> O <sub>6</sub> S)			
Calc.	C, 59.78;	H, 8.25;	N, 6.94
Found	C, 59.86;	H, 7.98;	N, 6.92

0.1 Na citrate, 1.65 dioxane

TLC: R<sub>f</sub> (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 9.24 min

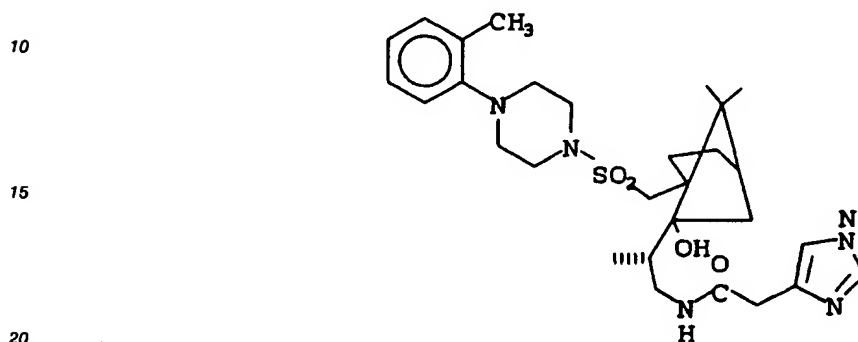
FAB MS: m/z 833 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.55 (br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.31 (s, 3H), 1.15 (s, 3H), 1.04 (s,

3H), 0.98 (d, J=6 Hz, 3H)

### Example 7

5 1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4(5-IMIDAZOLYLACETYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.34 mmol) in DMF (15 mL) was added 4(5)-imidazole acetic acid hydrochloride (679 mg; 4.18 mmol), BOP (1.85 g; 4.18 mmol), and DIEA (2.18 mL; 12.5 mmol). After 16 h, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated aqueous NaHCO<sub>3</sub> solution (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 92:8:0.8 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The title compound crystallized from EtOAc, mp 159-163°C.

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Anal: (C <sub>29</sub> H <sub>43</sub> N <sub>5</sub> O <sub>4</sub> S)			
Calc.	C, 62.45;	H, 7.77;	N, 12.56
Found	C, 62.88;	H, 7.68;	N, 12.79

35

TLC: R<sub>f</sub> 0.4 (90:10:1 CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH)

HPLC (method A): retention time 8.72 min

FAB MS: m/z 558 (M<sup>+</sup> + H)

40 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.57 (s, 1H), 7.2 (m, 3H), 7.0 (m, 2H), 6.88 (s, 1H), 3.55 (m, 2H), 3.4 (m, 5H), 2.95 (m, 4H), 2.87 (d, J=15 Hz, 1H), 2.31 (s, 3H), 1.71 (t, J=4 Hz, 1H), 1.52 (d, J=13 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.97 (d, J=6 Hz, 3H)

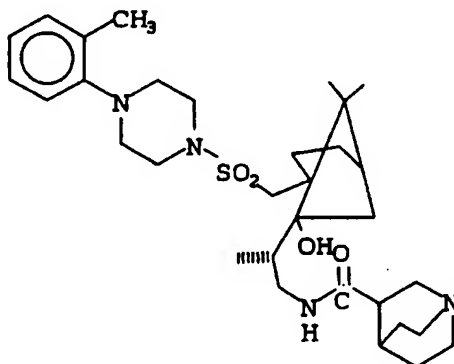
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## Exempl 8

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(QUINUCLIDIN-3-YL-CARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-*exo*-hydroxy-2-*endo*-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (2.00 g; 4.45 mmol) in DMF (50 mL) was added quinuclidine-3-carboxylic acid hydrochloride (938 mg; 4.90 mmol), BOP (2.17 g; 4.90 mmol), and DIEA (2.56 mL; 14.7 mmol). After 16 h, the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 1% acetic acid. The acetate salt of the title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

Anal: (C <sub>32</sub> H <sub>50</sub> N <sub>4</sub> O <sub>4</sub> S)			
Calc.	C, 60.39;	H, 8.58;	N, 8.39
Found	C, 60.41;	H, 8.19;	N, 8.58

0.8 CH<sub>3</sub>CO<sub>2</sub>H, 1.85 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.65 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

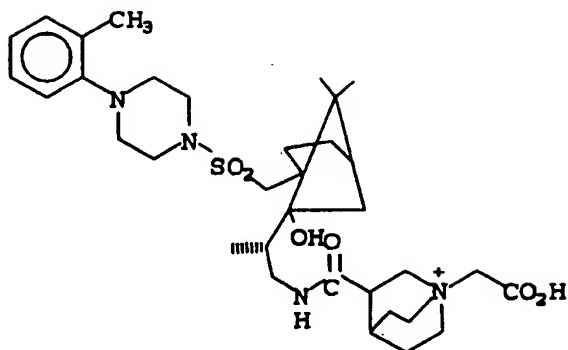
HPLC (method A): retention time 8.68 min

FAB MS: m/z 587 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.16 (s, 3H), 1.03 (overlapping s and d, 6H)

## Example 9

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(1-CARBOXYMETHYLQUINUCLIDIN-3-YL-CARBONYL)-AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(2-methylphenyl)piperazine-4-ylmethanesulfonyl)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; MW = 668; 2.25 mmol) in DMF (30 mL) was added iodoacetic acid (543 mg; 2.92 mmol) and DIEA (0.43 mL; 2.48 mmol). After 16 h, TLC showed complete consumption of starting material. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 1% acetic acid. The title compound, as a 1:1 mixture of diastereomers, was obtained as a lyophilized powder.

Anal: (C <sub>34</sub> H <sub>52</sub> N <sub>4</sub> O <sub>4</sub> S)			
Calc.	C, 60.52;	H, 8.18;	N, 8.04
Found	C, 60.52;	H, 7.98;	N, 8.15

0.55 CH<sub>3</sub>CO<sub>2</sub>H, 0.95 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.20 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

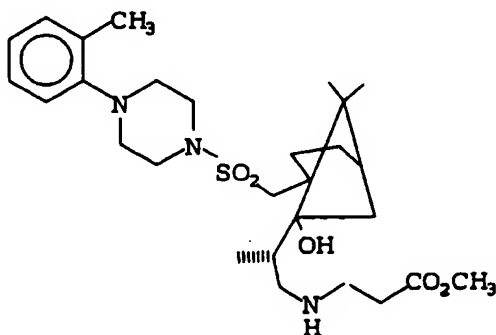
HPLC (method A): retention time 8.73 min

FAB MS: m/z 647 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (TFA salt; 400 MHz, CDCl<sub>3</sub>): δ 7.46 (br s, 1H), 7.19 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H), 0.98 (d, J = 6 Hz, 3H)

#### Example 10

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(2-METHOXYCARBONYLETHYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (100 mg; 0.22 mmol) in 1:1 DMF-MeOH (3 mL) was added methyl acrylate (0.020 mL; 0.22 mmol). After 16 h, the solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing

0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: (C <sub>28</sub> H <sub>45</sub> N <sub>3</sub> O <sub>5</sub> S)			
Calc.	C, 53.03;	H, 6.88;	N, 6.06
Found	C, 53.01;	H, 6.90;	N, 6.01

1.3 TFA, 0.5 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.35 (95:5 CHCl<sub>3</sub>:MeOH)

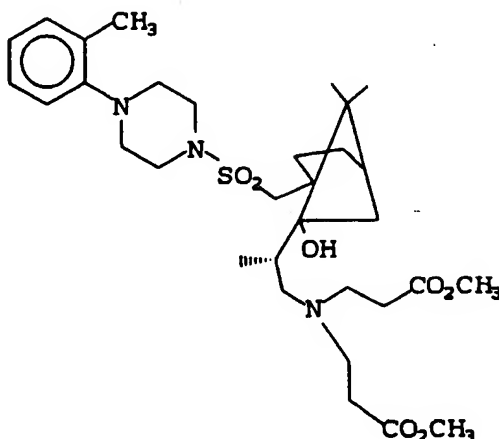
HPLC (method A): retention time 9.04 min

FAB MS: m/z 536 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.03 (m, 2H), 3.72 (s, 3H), 2.32 (s, 3H), 1.19 (d, J = 6 Hz, 3H), 1.15 (s, 3H), 0.98 (s, 3H)

#### EXAMPLE 11

1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-bis-(2-methoxycarbonyl)ethyl)amino)propylbicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (100 mg; 0.22 mmol) in 1:1 DMF-MeOH (3 mL) was added methyl acrylate (0.080 mL; 0.89 mmol). After 16 h, the solvents were removed under reduced pressure and the residue was purified by pressurized silica gel chromatography using 3:1 hexane-ethyl acetate as eluant. The title compound was obtained as a foam from hexane.

Anal: (C <sub>32</sub> H <sub>51</sub> N <sub>3</sub> O <sub>7</sub> S)			
Calc:	C 61.81,	H 8.27,	N 6.76
Found:	C 61.55,	H 8.13,	N 6.55

TLC: R<sub>f</sub> 0.40 (1:3 EtOAc:hexanes)

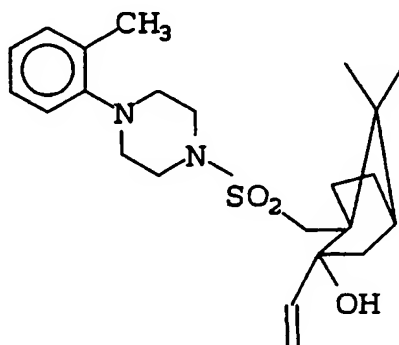
HPLC (method A): retention time 9.71 min

FAB MS: m/z 622 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 2H), 7.02 (m, 2H), 3.66 (s, 6H), 2.31 (s, 3H), 1.13 (s, 3H), 1.00 (overlapping a and d, 6H)

## EXAMPLE 12

1-((7,7-dimethyl-2-exo-hydroxy-2-endo-phenyl-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



To a  $-78^{\circ}\text{C}$  stirred 1.0 M solution of vinyl magnesium chloride in THF (25 mL; 25 mmol) was added a  $-78^{\circ}\text{C}$  solution of 1-((7,7-dimethyl-2-oxo-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (5.00 g; 12.8 mmol) in THF (100 mL) via cannula. The resulting solution was stirred under argon overnight, allowing the cooling bath to warm to ambient temperature. The reaction was quenched by addition of 2% aqueous HCl (50 mL), and the mixture was partitioned between ethyl acetate and water. The organic phase was washed with aqueous  $\text{NaHCO}_3$  and brine, dried over  $\text{MgSO}_4$ , and filtered. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel chromatography using 4:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from ether.

Anal: ( $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_3\text{S}$ ) 0.06 $\text{H}_2\text{O}$			
Calc:	C 65.82,	H 8.19,	N 6.67
Found:	C 65.99,	H 8.42,	N 6.63

TLC:  $R_f$  0.36 (1:5 EtOAc:hexanes)

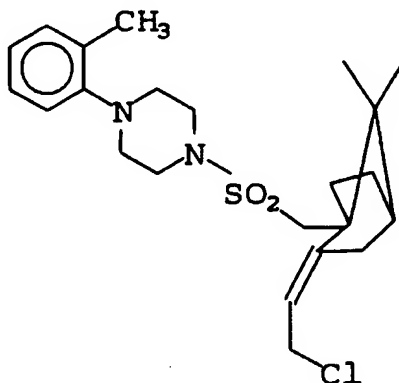
HPLC (method A): retention time 11.41 min

FAB MS:  $m/z$  419 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.20 (m, 2H), 7.02 (m, 2H), 6.48 (dd, 1H), 5.30 (d, 1H), 5.17 (d, 1H), 2.32 (s, 3H), 1.22 (s, 3H), 0.94 (s, 3H).

## EXAMPLE 13

1-((7,7-dimethyl-2-(2-chloro)ethylidene-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine



To a 0°C stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-ethenyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (2.90 g; 6.94 mmol) in THF (100 mL) was added triethylamine (1.50 mL; 10.7 mmol) and DMF (0.58 mL; 7.5 mmol). Thionyl chloride (0.66 mL; 9.1 mmol) was added dropwise, and the resulting solution was stirred for 18 h, allowing the cooling bath to warm ambient temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (150 mL) and washed with 5% aqueous HCl (75 mL), water (75 mL) and aqueous NaHCO<sub>3</sub> (100 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam.

Anal: (C <sub>23</sub> H <sub>33</sub> ClN <sub>2</sub> O <sub>2</sub> S) 0.6 H <sub>2</sub> O			
Calc:	C 65.82,	H 8.19,	N 6.67
Found:	C 65.99,	H 8.42,	N 6.63

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.03 (m, 2H), 5.87 (m, 1H), 2.32 (s, 3H), 1.00 (s, 3H), 0.82 (s, 3H)



## EXAMPLE 14

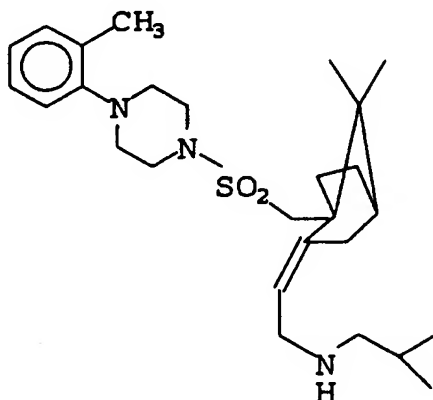
1-((7,7-dimethyl-2-(2-isobutylamino)ethylidene-bicyclo (2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methyl-phenyl) piperazine

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To a stirred solution of 1-((7,7-dimethyl-2-(2-chloro) ethylidene-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)peperazine (200 mg; 0.46 mmol) in MeOH (2 mL) was added isobutylamine (0.5 mL; 5 mmol). After being stirred fro 18 h, the solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

TLC:  $R_f$  0.30 (95:5:0.5  $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$ )

HPLC (method A): retention time 9.78 min

FAB MS:  $m/z$  474 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.20 (m, 3H), 7.03 (t, 1H), 5.78 (m, 1H), 2.35 (s, 3H), 1.13 (d,  $J = 7$  Hz, 6H), 1.12 (s, 3H), 0.88 (s, 3H)

## EXAMPLE 15

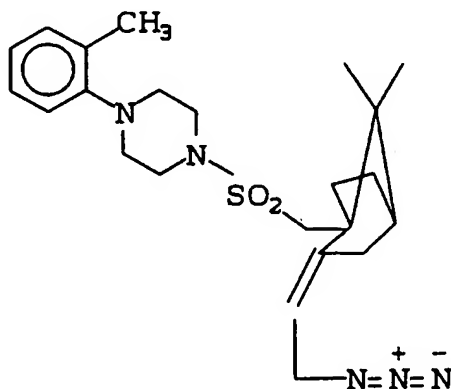
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1-((7,7-dimethyl-2-(2-azido)ethylidene-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine

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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-chloro)ethylidin -(2.2.1)bicycloheptan-1-yl)-methan sulfonyl)-4-(2-m thylphenyl)pip razine (3.58 g;8.19 mmol) in DMSO (50 mL) and THF (45 mL) was

add d a solution of sodium azid (5.3 g; 82 mmol) in water (20 mL). Aft r 24 h, the solvents were remov d und r reduced pr ssur , the residue was susp nd d in dichloromethane (100 mL) and washed with water (3 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure to give a solid.

Anal: (C <sub>23</sub> H <sub>33</sub> N <sub>5</sub> O <sub>2</sub> S)			
Calc:	C 62.27,	H 7.50,	N 15.79
Found:	C 62.41,	H 7.54,	N 15.60

TLC: R<sub>f</sub> 0.75 (70:30 hexane-ethylacetate)

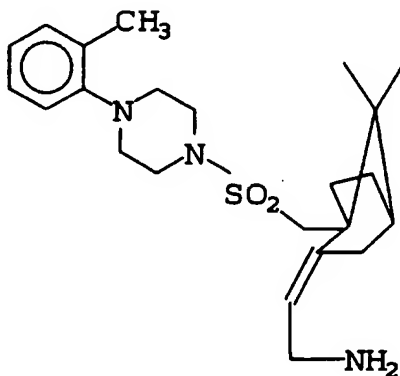
HPLC (method A): retention time 12.50 min

FAB MS: m/z 444 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.02 (m, 2H), 5.79 (m, 1H), 2.32 (s, 3H), 0.85 (s, 3H)

#### EXAMPLE 16

1-((7,7-dimethyl-2-(2-amino)ethylidene-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-azido)ethylidene-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (3.85 g; 8.69 mmol) in THF (150 mL) and water (3 mL) was added triphenylphosphine (2.50 g; 9.56 mmol). After 14 h, the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and extracted with 5% aqueous HCl (3 x 75 mL). The combined acid extracts were washed with ethyl acetate (50 mL) and then made basic by adding solid sodium hydroxide to pH 12. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 99:1 to 85:15 chloroform-methanol. The title compound was obtained as a solid.

Anal: (C <sub>23</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub> S) 0.5 H <sub>2</sub> O			
Calc:	C 64.75;	H 8.51;	N 9.85;
Found:	C 64.59;	H 7.51;	N 9.71

TLC: R<sub>f</sub> 0.56 (95:5:0.5 CHCl<sub>3</sub>-MeOH-NH<sub>4</sub> OH)

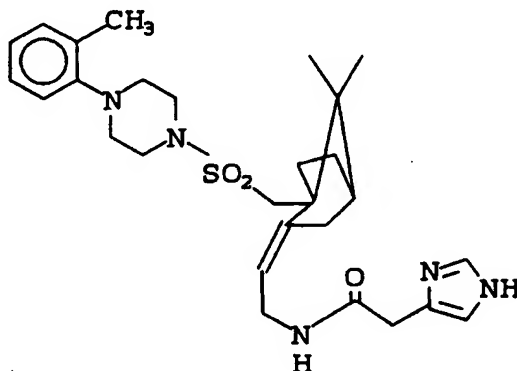
HPLC (method A): retention time 10.38 min

FAB MS: m/z 418 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.16 (m, 2H), 7.00 (m, 2H), 5.61 (m, 1H), 3.43 (m, 4H), 3.26 (d, J=6.6Hz, 2H), 1.18 (d, J=14.1 Hz, 1H), 1.97 (m, 4H), 2.92 (d, J=14.1 Hz, 1H), 2.35 (m, 1H), 2.31 (s, 3H), 1.7-1.8 (m, 3H), 1.70 (m, 1H), 1.25 (m, 1H), 0.99 (s, 3H), 0.81 (s, 3H).

## EXAMPLE 17

1-((7,7-dimethyl-2-(2-(4(5)-imidazolylacetyl)amino) ethylidene-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-amino)ethylidene-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.48 mmol) in DMF (5 mL) was added BOP (265 mg; 0.60 mmol), 4-imidazoleacetic acid hydrochloride (115 mg; 0.72 mmol) and DIEA (0.38 mL; 2.2 mmol). After 14 h, the solvents were removed under reduced pressure, the residue was suspended in ethyl acetate (50 mL) and washed with aqueous  $\text{NaHCO}_3$  (2 x 25 mL) and water (2 x 25 mL). The organic phase was dried ( $\text{MgSO}_4$ ), filtered and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPCL using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: ( $\text{C}_{28}\text{H}_{39}\text{N}_5\text{O}_3\text{S}$ ); 0.5  $\text{H}_2\text{O}$ ; 2.0 TFA;

Calc:	C 50.38;	H 5.55;	N 9.18
Found:	C 50.40;	H 5.55;	N 9.40

TLC:  $R_f$  0.42 (95:5:0.5  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ )

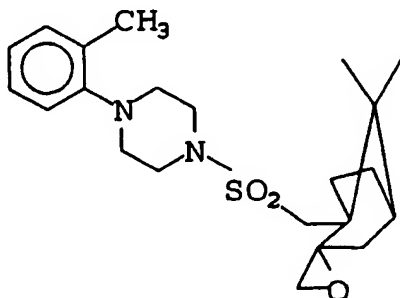
HPLC (method A): retention time 8.76 min.

FAB MS:  $m/z$  526 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.40 (s, 1H), 7.58 (br m, 1H), 7.22 (m, 3H), 7.10 (m, 2H), 5.57 (br t, 1H), 2.37 (s, 3H), 0.97 (s, 3H), 0.76 (s, 3H)

## Example 18

1-((7,7-DIMETHYL-2-SPIRO-EPOXY-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred 0°C suspension of trimethylsulfoxonium iodide (6.78 g; 30.8 mmol) in THF (100 mL) was added n-butyllithium (11.1 mL of a 2.5 M solution in hexane; 27.7 mmol). After 4 h at 0°C, a solution of 1-((7,7-dimethyl-2-oxo-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (8.00 g; 20.5 mmol) in THF (50 mL). The resulting solution was stirred at 0°C for 2 h, and then at ambient temperature for 18 h. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate (150 mL) and washed with water (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The resulting solid was recrystallized from ether to give the title compound, as white needles.

Anal: (C <sub>22</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S)			
Calc.	C, 65.31;	H, 7.97;	N, 6.92
Found	C, 65.09;	H, 7.99;	N, 6.86

0.5 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.62 (4:1 hexane-ethyl acetate)

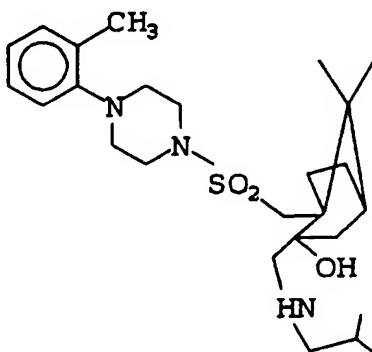
HPLC (method A): retention time 11.50 min

FAB MS: m/z 405 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.02 (m, 2H), 3.20 (d, J=5.4 Hz, 1H), 2.70 (d, J=5.4 Hz, 1H), 2.30 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H)

#### Example 19

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-ISOBUTYLAMINOMETHYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-(spiroepoxy)-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (200 mg; 0.495 mmol) in MeOH (3 mL) was added isobutylamine (0.5 mL; 5 mmol). After being stirred for 18 h, the solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 98:2:0.2 chloroform-methanol-NH<sub>4</sub>OH as eluant. The product was dissolved in methanol and to it was added several drops of 5% aqueous HCl. The solvents were removed under reduced pressure and the residue was triturated in ether to give the hydrochloride salt of the title compound as a white powder.

Anal: (C <sub>26</sub> H <sub>43</sub> N <sub>3</sub> O <sub>3</sub> S)			
Calc.	C, 57.00;	H, 8.76;	N, 7.67
Found	C, 57.03;	H, 8.84;	N, 7.61

1.0 HCl, 1.8 H<sub>2</sub>O

TLC (free base): R<sub>f</sub> 0.20 (3:1 hexane-ethyl acetate)

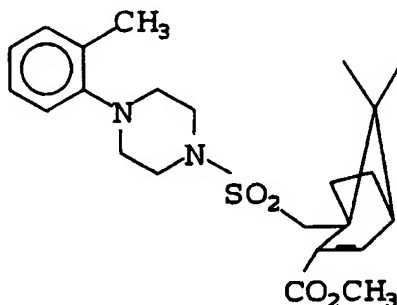
HPLC (method A): retention time 9.54 min

FAB MS:  $m/z$  478 ( $M^+ + H$ )

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.20 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.90 (two doublets, 6H)

# 5 Example 20

1-((7,7-DIMETHYL-2-METHOXYCARBONYL-BICYCLO (2.2.1)HEPT-2-EN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred, 0°C solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (10.0 g; 25.6 mmol) in dichloromethane (500 mL) was added 2,6-di-*t*-butyl-4-methylpyridine (7.8 g; 38 mmol) and trifluoromethanesulfonic anhydride (5.4 mL; 32 mmol). The cooling bath was removed and the solution was stirred for 18 h. The mixture was filtered and the filtrate was washed with 5% aqueous HCl (2 x 100 mL), water (100 mL), and aqueous  $NaHCO_3$  (2 x 100 mL). The organic phase was dried ( $MgSO_4$ ), filtered and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 9:1 hexane-ethyl acetate as eluant. The enol triflate product was obtained as a white foam and used as such in the next step. To a stirred solution of 1-((7,7-dimethyl-2-trifluoromethanesulfonyloxy-bicyclo(2.2.1)hept-2-en-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (10.5 g; 20.1 mmol) in 1:1 DMF-MeOH (150 mL) was added triethylamine (5.9 mL; 43 mmol), triphenylphosphine (317 mg; 1.21 mmol), and palladium(II)acetate (135 mg; 0.603 mmol). Carbon monoxide gas was bubbled through the solution for 15 min, and the reaction was kept under atmospheric pressure of CO for 18 h. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 9:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from hexane.

Anal: ( $C_{23}H_{32}N_2O_4S$ )			
Calc.	C, 62.14;	H, 7.50;	N 6.30
Found	C, 61.65;	H, 7.17;	N, 6.12

0.67  $H_2O$

TLC:  $R_f$  0.36 (1:5 EtOAc:hexanes)

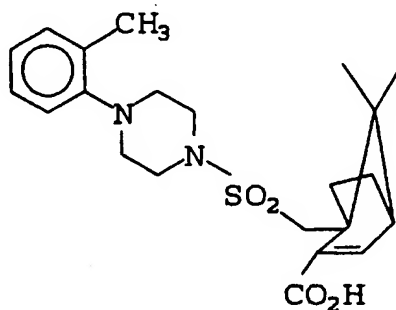
HPLC (method A): retention time 11.34 min

FAB MS:  $m/z$  433 ( $M^+ + H$ )

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.20 (m, 2H), 7.03 (m, 2H), 6.88 (d,  $J=3$  Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H)

Example 21

1-((7,7-DIMETHYL-2-CARBOXY-BICYCLO(2.2.1) HEPT-2-EN-1-YL)METHANESULFONYL)-4-(2-METHYL-PHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-methoxycarbonyl-bicyclo(2.2.1)hept-2-en-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.0 g; 2.3 mmol) in MeOH (10 mL) was added a solution of 4 M aqueous KOH (2.0 mL; 8.0 mmol). After 18 h, the reaction was brought to pH 1 with 5% aqueous HCl, and the solvents were removed under reduced pressure. The residue was taken up in chloroform (50 mL) and washed with water (25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure to give the hydrochloride salt of the title compound as a white foam.

Anal: (C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub> S)			
Calc.	C, 57.51;	H, 6.91;	N, 6.10
Found	C, 57.40;	H, 6.87;	N, 6.01

1.0 HCl, 0.25 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.59 (92:8:0.1 CHCl<sub>3</sub>:MeOH:HOAc)

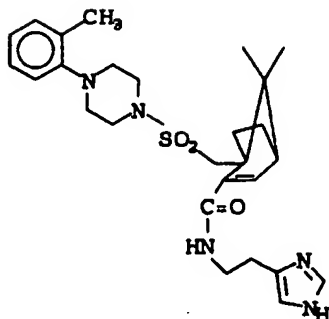
HPLC (method A): retention time 9.77 min

FAB MS: m/z 419 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.30 (m, 3H), 7.20 (t, 1H), 6.89 (d, J = 3 Hz, 1H), 2.43 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H)

Example 22

1-((7,7-DIMETHYL-2-(4-IMIDAZOLYL)ETHYLAMINOCARBONYL-BICYCLO(2.2.1)HEPT-2-EN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-carboxy-bicyclo(2.2.1)hept-2-en-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (100 mg; FW = 460; 0.22 mmol) in DMF (5 mL) was added histamine (30 mg; 0.27 mmol), BOP (115 mg; 0.25 mmol) and DIEA (0.12 mL; 0.69 mmol). After 18 h, the solvent was removed under reduced pressure, the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: (C <sub>27</sub> H <sub>37</sub> N <sub>5</sub> O <sub>3</sub> S)			
Calc.	C, 49.35;	H, 5.31;	N, 9.22
Found	C, 49.25;	H, 5.39;	N, 9.20

2.1 TFA, 0.45 H<sub>2</sub>O

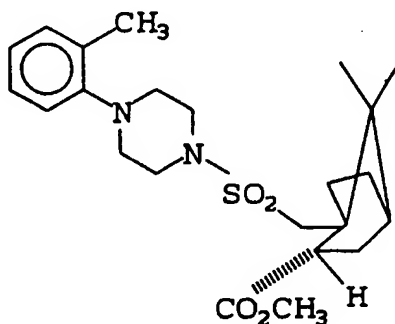
HPLC (method A): retention time 8.16 min

FAB MS: m/z 512 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.80 (s, 1H), 7.40 (s, 1H), 7.18 (m, 2H), 7.05 (d, 1H), 6.99 (t, 1H), 6.41 (d, J = 3 Hz, 1H), 2.31 (s, 3H), 1.08 (s, 3H), 0.98 (s, 3H)

#### Example 23

1-((7,7-DIMETHYL-2-ENDO-METHOXYCARBONYL-BICYCLO (2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred, -78°C solution of 1-((7,7-dimethyl-2-methoxycarbonyl-bicyclo(2.2.1)hept-2-en-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (3.0 g; 6.9 mmol) in 2:1 THF-MeOH (50 mL) was added a solution of 0.1 M samarium(II) iodide in THF (250.0 mL; 25.0 mmol). After 1 h, the reaction was warmed to ambient temperature and stirred for another 1 h. The solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The layers were separated and the organic phase was washed with water (50 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness under reduced pressure. By <sup>1</sup>H NMR analysis, a 6:1 ratio of endo:exo products was obtained. The major, lower R<sub>f</sub> isomer (endo) was obtained in pure form by pressurized silica gel column chromatography using a gradient elution of 98:2 to 95:5 hexane-ethyl acetate, followed by crystallization from ethyl acetate. The title compound was obtained as white needles.

Anal: (C <sub>23</sub> H <sub>34</sub> N <sub>2</sub> O <sub>4</sub> S)			
Calc.	C, 63.56;	H, 7.89;	N, 6.45
Found	C, 63.31;	H, 7.83;	N, 6.43

TLC: R<sub>f</sub> 0.44 (1:5 EtOAc:hexanes)

HPLC (method A): retention time 11.75 min

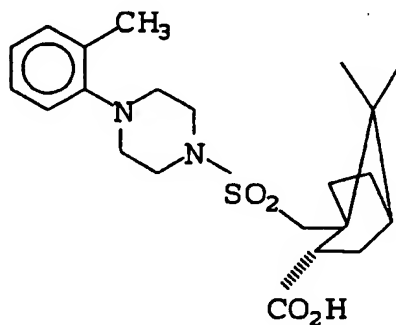
FAB MS: m/z 435 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.05 (m, 2H), 3.72 (s, 3H), 3.29 (ddd, 1H), 2.34 (s, 3H), 1.13 (s,

3H), 1.06 (s, 3H)

#### Example 24

#### 5 1-((7,7-DIMETHYL-2-ENDO-CARBOXY-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-endo-methoxycarbonyl-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.0 g; 2.3 mmol) in THF (10 mL) was added a solution of 4 M aqueous NaOH (1.5 mL; 6.0 mmol). The reaction was heated to reflux for 72 h, cooled, and brought to pH 1 with 5% aqueous HCl. The solvents were removed under reduced pressure and the residue was partitioned between chloroform and water. The organic phase was separated and washed with water, dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The title compound was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound was obtained as a lyophilized powder.

Anal: (C <sub>22</sub> H <sub>32</sub> N <sub>2</sub> O <sub>4</sub> S)			
Calc.	C, 51.92;	H, 5.99;	N, 4.94
Found	C, 51.92;	H, 5.95;	N, 5.17

1.25 TFA, 0.2 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.22 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 10.67 min

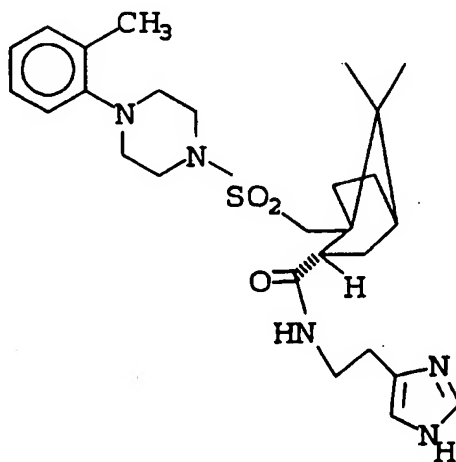
FAB MS: m/z 421 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.18 (m, 2H), 7.05 (d, 1H), 6.98 (t, 1H), 2.30 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H)



## Exempl 25

1-((7,7-DIMETHYL-2-ENDO-(4-IMIDAZOLYL)ETHYLAMINOCARBONYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-endo-carboxy-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (100 mg; 0.238 mmol) in DMF (5 mL) was histamine (35 mg; 0.32 mmol), BOP (142 mg; 0.321 mmol), and DIEA (0.13 mL; 0.75 mmol). After 18 h, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>27</sub> H <sub>39</sub> N <sub>5</sub> O <sub>3</sub> S)			
Calc.	C, 46.66;	H, 5.58;	N, 8.58
Found	C, 46.63;	H, 5.23;	N, 8.97

2.35 TFA, 1.9 H<sub>2</sub>O

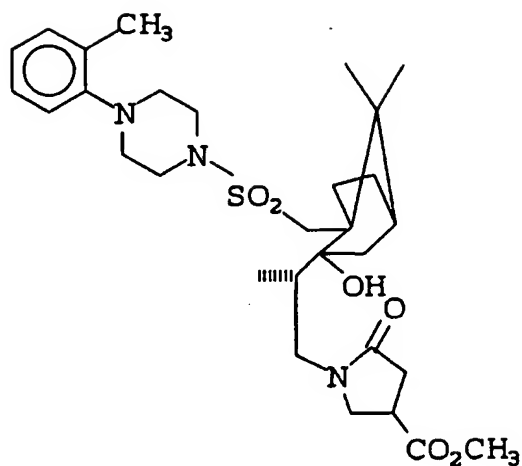
HPLC (method A): retention time 8.99 min

FAB MS: m/z 514 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.40 (s, 1H), 7.1-7.3 (m, 5H), 2.39 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H)

## Example 26

TWO ISOMERS OF 1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-METHOXYCARBONYL)-2-PYRROLIDINON-1-YL)PROPYLBICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (250 mg; 0.557 mmol) in methanol (3 mL) was added dimethyl itaconate (200 mg; 1.27 mmol). The reaction was heated to reflux for 18 h. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 35:65 hexane-ethyl acetate as eluant. The products were obtained as white foams.

Isomer 1:

Anal: (C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>6</sub> S)			
Calc.	C, 62.58;	H, 7.88;	N, 7.30
Found	C, 62.58;	H, 8.03;	N, 6.95

TLC: R<sub>f</sub> 0.34 (35:65 hexane-ethyl acetate)

HPLC (method A): retention time 10.23 min

FAB MS: m/z 576 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.18 (m, 2H), 7.01 (m, 2H), 3.76 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.95 (d, J = 6 Hz, 3H)

Isomer 2:

Anal: (C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>6</sub> S)			
Calc.	C, 62.58;	H, 7.88;	N, 7.30
Found	c, 62.43;	H, 8.07;	N, 6.95

TLC: R<sub>f</sub> 0.23 (35:65 hexane-ethyl acetate)

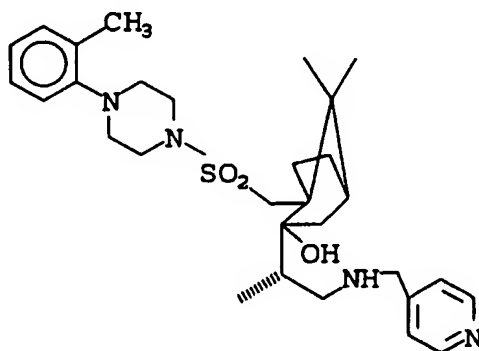
HPLC (method A): retention time 10.24 min

FAB MS: m/z 576 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.03 (m, 2H), 3.74 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.95 (d, J = 6 Hz, 3H)

## Example 27

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-PYRIDINYL)METHYLAMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazine (50 mg; 0.11 mmol) in DMF (2 mL) was added 4-chloromethylpyridine hydrochloride (18 mg; 0.11 mmol) and potassium carbonate (50 mg; 0.36 mmol). The reaction was heated to 80°C 18 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>30</sub> H <sub>44</sub> N <sub>4</sub> O <sub>3</sub> S)			
Calc.	C, 52.07;	H, 5.89;	N, 7.06
Found	C, 52.06;	H, 5.86;	N, 7.20

2.2 TFA, 0.1 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.X

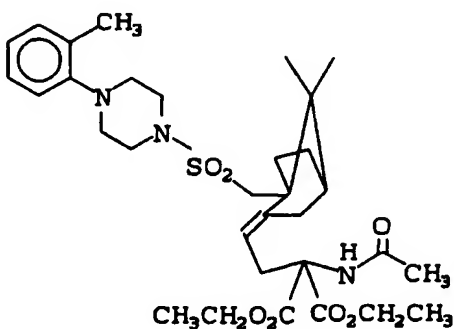
HPLC (method A): retention time 8.15 min

FAB MS: m/z 541 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.72 (br s, 2H), 7.85 (br s, 2H), 7.20 (m, 2H), 7.03 (m, 2H), 4.27 (AB quartet, 2H), 2.31 (s, 3H), 1.14 (s, 3H), 0.95 (overlapping s and d, 6H)

## Example 28

1-((7,7-DIMETHYL-2-(3-ACETAMIDO-3'-DI(ETHOXYCARBONYL))PROPYLIDINE-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of di thyl ac tamidomalonat (0.69 g; 3.2 mmol) in DMF (20 mL) was added NaH (125 mg of a 60% dispersion in min ral oil; 3.13 mmol). After 30 min, 1-((7,7-dimethyl-2-(2-chloro) thylidine-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylph nyl)piperazine (0.35 g; 0.80 mmol) was added and the mixture was warmed to 50°C for 3 h. The mixture was cooled and acetic acid (1.5 mL) was added. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 25 mL). The organic phase was dried, filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam.

Anal: (C <sub>32</sub> H <sub>47</sub> N <sub>3</sub> O <sub>7</sub> S)			
Calc.	C, 62.32;	H, 7.51;	N, 6.81
Found	C, 61.96;	H, 7.71;	N, 6.55

TLC: R<sub>f</sub> 0.36 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

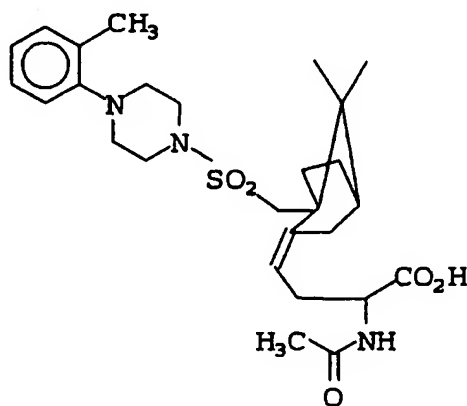
HPLC (method A): retention time 11.54 min

FAB MS: m/z 618 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.03 (m, 2H), 6.78 (s, 1H), 5.38 (br t, 1H), 4.22 (m, 4H), 2.32 (s, 3H), 2.00 (s, 3H), 1.27 (t, J = 7 Hz, 3H), 1.24 (t, J = 7 Hz, 3H), 0.97 (s, 3H), 0.78 (s, 3H)

#### Example 29

1-((7,7-DIMETHYL-2-(3-ACETAMIDO-3-CARBOXY) PROPYLIDINE-BICYCLO(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-(3-acetamido-3,3'-di(ethoxycarbonyl))propylidine-(2.2.1) bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) -piperazine (0.10 g; 0.16 mmol) in ethanol (2 mL) was added a solution of 2 M NaOH (0.30 mL; 0.60 mmol) and the mixture was heated to reflux for 6 h. The mixture was cooled and brought to pH 2 with 5% aqueous HCl. The mixture was heated to reflux for 1 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound, as a 1:1 mixture of diastereomers, was obtained as a lyophilized powder.

Anal: (C <sub>27</sub> H <sub>33</sub> N <sub>3</sub> O <sub>5</sub> S)			
Calc.	C, 54.37;	H, 6.53;	N, 6.56
Found	C, 54.26;	H, 6.41;	N, 6.59

1.0 TFA, 0.5 H<sub>2</sub>O

TLC: R<sub>f</sub> 0.39 (92:8:0.1 CHCl<sub>3</sub>:MeOH:HOAc)

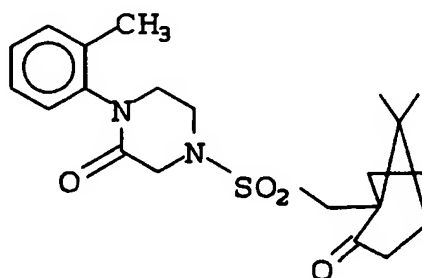
HPLC (method A): retention time 9.62 min

FAB MS:  $m/z$  518 ( $M^+ + H$ )

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.25 (m, 4H), 7.13 (m, 4H), 6.52 (d, 1H), 6.40 (d, 1H), 5.45 (m, 1H), 5.40 (m, 1H), 4.67 (m, 2H), 2.40 (s, 6H), 20.5 (s, 3H), 2.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H), 0.79 (s, 3H)

### EXAMPLE 30

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-t-butyloxycarbonyl-4-(2-methylphenyl)-3-piperazinone (0.25 g; 0.86 mmol) in dichloromethane (3 mL) was added TFA (1 mL). After 1 hour the solvents were removed under reduced pressure and the residue was taken up into chloroform and evaporated several times to remove excess TFA. The residue was dissolved in chloroform (5 mL) and added to the stirred solution was 10-camphorsulfonyl chloride (376 mg; 1.50 mmol) and triethylamine (0.38 mL; 2.7 mmol). After 12 hours, the mixture was diluted with chloroform (25 mL) and extracted with 5% aqueous HCl (25 mL), water (25 mL), and aqueous  $NaHCO_3$  (25 mL). The organic phase was dried ( $MgSO_4$ ), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from ether-hexane.

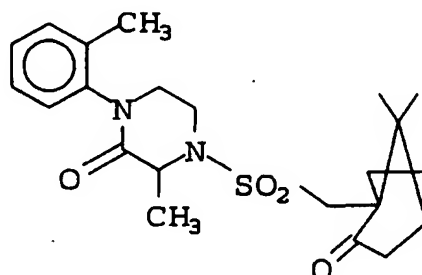
Anal: ( $C_{21}H_{28}N_2O_4S$ )			
Calc.	C, 62.35;	H, 6.98;	N, 6.93
Found	C, 61.78;	H, 6.98;	N, 6.82

TLC:  $R_f$  0.30 (1:1 hexane-ethyl acetate)

HPLC (method A): retention time 8.15 min

FAB MS:  $m/z$  405 ( $M^+ + H$ )

## EXAMPLE 31

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-2-METHYL-3-PIPERAZINONE

To a stirred 78°C solution of LDA (2.0 mmol) in THF (15 mL) was added a -78°C solution of 1-t-butylloxycarbonyl-4-(2-methylphenyl)-3-piperazinone (0.50 g; 1.7 mmol) in THF (5 mL). The resulting solution was stirred for 1 hour, when iodomethane (0.125 mL; 2.0 mmol) was added. The reaction mixture was stirred at -78°C for 30 minutes, and then the cooling bath was removed and the mixture was stirred at ambient temperature for 3 hours. Water (10 mL) and ethyl acetate (50 mL) were added. The organic layer was separated and washed with water (25 mL) and brine (25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 85:15 hexane-ethyl acetate as eluant. The methylated product had an R<sub>f</sub> = 0.47 (70:30 hexane-ethyl acetate) and an HPLC retention time of 8.32 min (Method A). The product (0.40 g; 1.3 mmol) was dissolved in chloroform (3 mL) and TFA (1 mL) was added. After 2 hours, the mixture was diluted with chloroform (50 mL) and extracted with aqueous NaHCO<sub>3</sub> (3 x 25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure to give an oil (HPLC retention time 2.95 min, Method A). The residue was dissolved in chloroform (20 mL) and to the stirred solution was added 10-camphorsulfonyl chloride (0.41 g; 1.6 mmol) and triethylamine (0.28 mL; 2.0 mmol). After 12 hours, the mixture was diluted with chloroform (25 mL) and extracted with 5% aqueous HCl (25 mL), water (25 mL), and aqueous NaHCO<sub>3</sub> (2 x 25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound, as a 1:1 mixture of diastereomers, was obtained as a white solid from hexane-ether.

Anal: (C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub> S)			
Calc.	C, 63.13;	H, 7.23;	N, 6.69
Found	C, 63.46;	H, 7.09;	N, 6.74

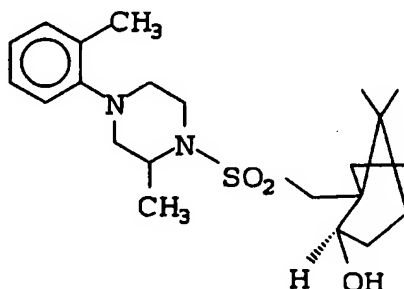
TLC: R<sub>f</sub> 0.27 (60:40 hexane-ethyl acetate)

HPLC (method A): retention time 8.52 min

FAB MS: m/z 419 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.1-7.3 (m, 8H), 4.62 (overlapping quartets, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.68 (overlapping doublets, 6H), 1.13 (s, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H)

## EXAMPLE 32

1-((7,7-DIMETHYL-2-EXO-HYDROXY-BICYCLO(2.2.1)-HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-2-METHYL-PIPERAZINE

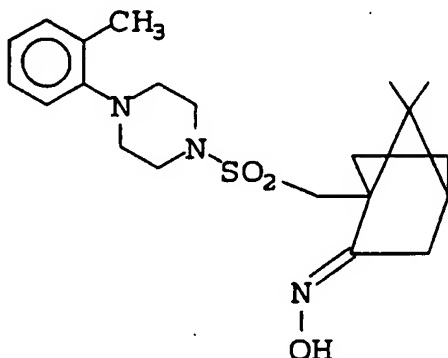
To a stirred, 0°C solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-2-methyl-3-piperazinone (0.15 g; 0.36 mmol) in THF (5 mL) was added a 1.0 M solution of LAH in THF (1.1 mL; 1.1 mmol). The resulting solution was warmed to ambient temperature and stirred for 3 hours. The reaction was quenched by adding aqueous NaOH to give a white precipitate. The mixture was diluted with ethyl acetate and the solids were removed by filtration through Celite. The filtrate solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 9:1 hexane-ethyl acetate as eluant to give 1-((7,7-dimethyl-2-exo-hydroxy-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-2-methyl-2,3-dehydro-piperazine (FAB MS: m/z 405 ( $M^+ + H$ ); olefinic proton at 5.8 ppm in the  $^1H$  NMR spectrum). This product (75 mg; 0.19 mmol) was dissolved in triethylsilane (2 mL) and to the stirred solution was added TFA (0.030 mL; 0.38 mmol). After 18 hours, the solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and washed with aqueous  $NaHCO_3$  (2 x 10 mL). The organic phase was dried ( $MgSO_4$ ), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound, as a 1:1 mixture of diastereomers, was obtained as a lyophilized powder.

Anal: (C <sub>22</sub> H <sub>34</sub> N <sub>2</sub> O <sub>3</sub> S)			
Calc.	C, 63.13;	H, 7.23;	N, 6.69
Found	C, 63.46;	H, 7.09;	N, 6.74

TLC:  $R_f$  0.27 (60:40 hexane-ethyl acetate)  
HPLC (method A): retention time 14.33 min  
FAB MS: m/z 407 ( $M^+ + H$ )  
 $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.20 (m, 4H), 7.06 (m, 4H), 4.20 (m, 2H), 2.36 (s, 6H), 1.55 (overlapping doublets, 6H), 1.09 (s, 6H), 0.86 (s, 6H)

## EXAMPLE 33

1-((7,7-DIMETHYL-2-OXIMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (65.0 g; 166 mmol) in pyridine (250 mL) was added hydroxylamine hydrochloride (35.0 g; 0.504 mol). The solution was heated to 70 °C for 18 h. The solvent was removed under reduced pressure, the residue was taken up in chloroform (500 mL) and washed with aqueous NaHCO<sub>3</sub> (2 x 200 mL), water (100 mL), and 5% aqueous HCl (2 x 200 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The title compound crystallized from ethyl acetate, giving off-white needles (57 g; 84%), mp 174-175 °C.

Anal: (C <sub>21</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> S)			
Calc.	C, 62.19;	H, 7.71;	N, 10.36
Found	C, 62.29;	H, 7.63;	N, 10.15

TLC: R<sub>f</sub> 0.40 (75:25 hexane-ethyl acetate)

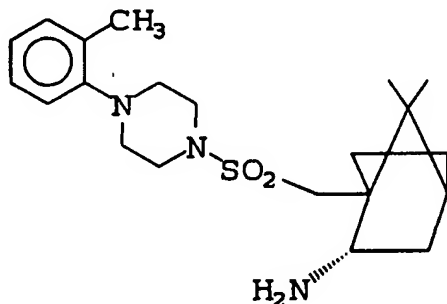
HPLC (method A): retention time 9.98 min

FAB MS: m/z 406 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90 (br s, 1H), 7.18 (m, 2H), 7.02 (m, 2H), 3.47 (m, 4H), 4.43 (d, J = 14.4 Hz, 1H), 3.00 (m, 4H), 2.92 (d, J = 14.4 Hz, 1H), 2.4-2.6 (m, 2H), 2.31 (s, 3H), 2.09 (d, J = 16.9 Hz, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.32 (m, 1H), 1.08 (s, 3H), 0.87 (s, 3H)

## EXAMPLE 34

1-((7,7-DIMETHYL-2-ENDO-AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



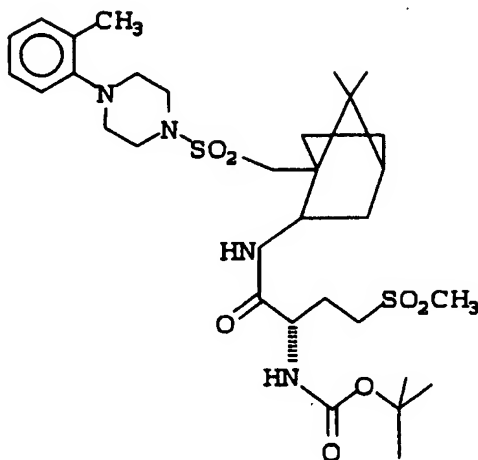


To a stirred solution of 1-((7,7-dimethyl-2-oximino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (35.0 g; 86 mmol) in 2-methoxyethanol (500 mL) containing Raney Nickel alloy (105.0 g) was added sodium hydroxide solution (17.2 g; 430 mmol dissolved in 75 mL) dropwise over 30 min. During the addition heat and gas was evolved. The mixture was stirred at ambient temperature for 16 h, at which time TLC indicated complete consumption of starting oxime and a ca. 4:1 mixture of endo (lower Rf) and exo (higher Rf) amine products. The mixture was filtered through Celite and the filter-cake was washed with methanol and ethyl acetate. The solvents were removed under reduced pressure and the resulting solid was dispersed in water and filtered. The dried solid was purified by pressurized silica gel column chromatography, using a 93:3 to 94:6 A:B gradient elution (A = chloroform, B = 5% NH<sub>4</sub>OH/MeOH). The title compound was obtained as a white foam (24 g; 70%).

FAB MS: m/z 392 (M<sup>+</sup> + H)

#### EXAMPLE 35

1-((7,7-DIMETHYL-2-ENDO-(2S-(TERT-BUTYLOXYCARBONYLAMINO)-4-(METHYLSULFONYL)-BUTYRAMIDO)-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (2.0 g; 5.1 mmol) in DMF (20 mL) was added Na-Boc-L-methionine sulfone (1.5 g; 5.3 mmol), BOP reagent (2.5 g; 5.6 mmol), followed by DIEA (1.85 mL; 10.6 mmol). After being stirred at ambient temperature for 1 h, more DIEA (ca. 0.1 mL) was added to obtain a pH 8 solution. The solution was stirred for another 1 h, when the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with 5% aqueous HCl (2 x 50 mL), water (2 x 50 mL), and aqueous NaHCO<sub>3</sub> (2 x 75 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 4:1 EtOAc-hexanes as eluant. The title compound was obtained as a solid from methanol (2.8 g; 85%).

Anal: (C<sub>31</sub>H<sub>50</sub>N<sub>4</sub>O<sub>7</sub>S<sub>2</sub>)

Calc.	C, 55.78;	H, 7.76;	N, 8.39	0.7 H <sub>2</sub> O
Found	C, 55.57;	H, 7.70;	N, 8.36	

TLC: R<sub>f</sub> 0.73 (95:5 CHCl<sub>3</sub>:MeOH)

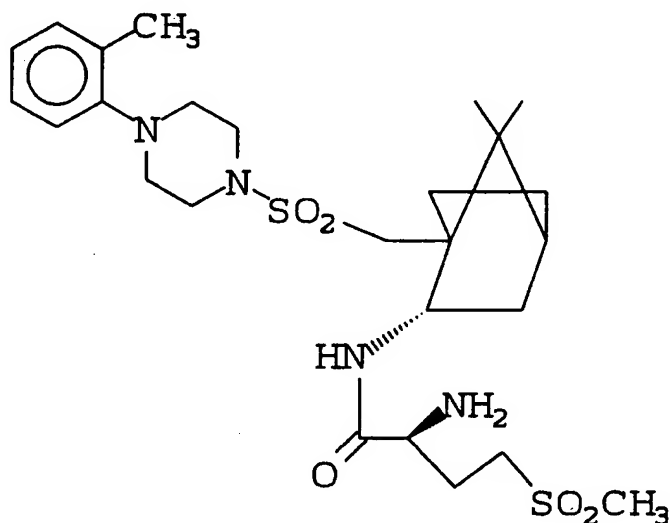
HPLC (method A): retention time 11.02 min

FAB MS: m/z 655 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 2H), 7.04 (m, 2H), 5.38 (br d, 1H), 4.32 (q, J = 7.4 Hz, 1H), 4.22 (m, 1H), 2.94 (s, 3H), 2.32 (s, 3H), 1.45 (s, 9H), 1.00 (s, 3H), 0.98 (s, 3H)

## EXAMPLE 36

1-((7,7-DIMETHYL-2-ENDO-(2S-AMINO-4-(METHYLSULFONYLBUTYRAMIDO)-BICYCLO(2.2.1)HEPTAN-1-  
YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-tert-butyloxycarbonylamino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (2.5 g; 3.8 mmol) in dichloromethane (15 mL) was added TFA (5 mL). After 1 h, the solvents were removed under reduced pressure. The residue was dissolved in chloroform (100 mL) and washed with aqueous NaHCO<sub>3</sub> (2 x 75 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The title compound was obtained as a white foam from EtOAc (1.9 g; 90%).

Anal: (C<sub>26</sub>H<sub>42</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub>)

Calc.	C, 56.14;	H, 7.75;	N, 9.29	0.55 EtOAc
Found	C, 55.94;	H, 7.74;	N, 9.31	

TLC: R<sub>f</sub> 0.17 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

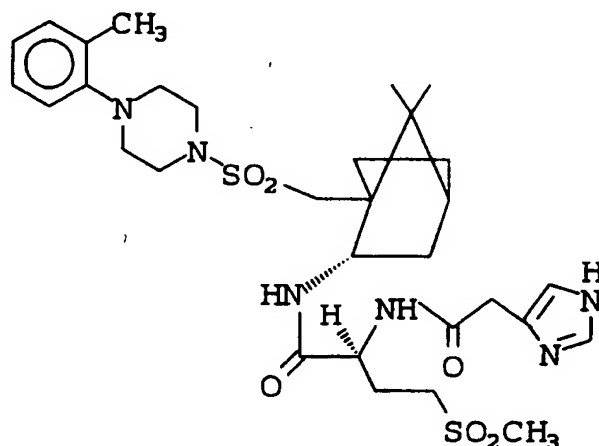
HPLC (method A): retention time 8.50 min

FAB MS: m/z 455 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.67 (d, J = 8.4 Hz, 1H), 7.20 (m, 2H), 7.02 (m, 2H), 4.43 (m, 1H), 2.94 (s, 3H), 2.31 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H)

## EXAMPLE 37

1-((7,7-DIMETHYL-2-ENDO-(2S-(IMIDAZOL-4-YLACETYLAMINO)-4-(METHYLSULFONYL)BUTYRAMIDO)-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo-(2.2.1)-  
 25 heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (250 mg; 0.45 mmol) in DMF (5 mL) was added  
 4-imidazole acetic acid hydrochloride (110 mg; 0.68 mmol), BOP (265 mg; 0.60 mmol), and DIEA (0.355  
 mL; 2.0 mmol). The solution was stirred at ambient temperature for 18 h. The solvent was removed under  
 reduced pressure, and the residue was suspended in EtOAc (100 mL) and filtered through Celite to remove  
 red polymer. The filtrate was washed with 5% aqueous HCl (50 mL), water (50 mL), and aqueous NaHCO<sub>3</sub>  
 30 (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced  
 pressure. The residue was purified by pressurized silica gel column chromatography using 92:8:0.8  
 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The title compound was obtained as a solid from EtOAc (230 mg; 78%).

Anal: (C<sub>31</sub>H<sub>46</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>)

Calc.	C, 53.74;	H, 7.32;	N, 11.26	0.6 EtOAc,	1.7H <sub>2</sub> O
Found	C, 53.74;	H, 7.00;	N, 11.25		

TLC: R<sub>f</sub> 0.22 (90:10:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

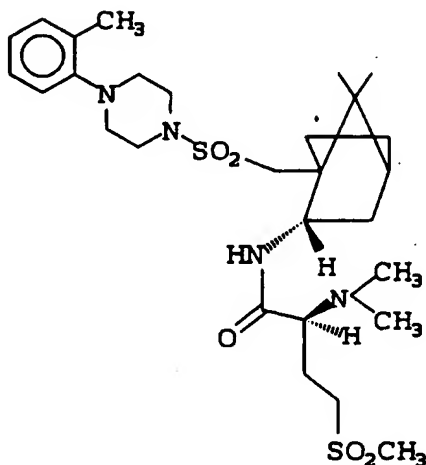
HPLC (method A): retention time 8.49 min

FAB MS: m/z 663 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.73 (overlapping singlet and broad singlet, 2H), 7.38 (br d, 1H), 7.18 (m, 2H),  
 7.02 (m, 2H), 6.96 (s, 1H), 4.68 (br q, J = ca. 5 Hz, 1H), 4.27 (m, 1H), 3.62 (br s, 2H), 2.92 (s, 3H), 2.30 (s,  
 45 3H), 1.00 (s, 3H), 0.98 (s, 3H)

## EXAMPLE 38

1-((7,7-DIMETHYL-2-ENDO-(2S-(DIMETHYLAMINO)-4-(METHYLSULFONYL)BUTYRAMIDO)-BICYCLO-(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo-(2.2.1)-heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (250 mg; 0.45 mmol) in 1:1 HOAc:MeOH (10 mL) was added 37% aqueous formaldehyde (2 mL) and NaBH<sub>3</sub>CN (60 mg; 0.95 mmol). The solution was stirred at ambient temperature for 4 h. Aqueous NaHCO<sub>3</sub> (2 mL) was added and the solvents were removed under reduced pressure. The residue was suspended in EtOAc (75 mL) and washed with water (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The title compound was obtained as a white foam from EtOAc (190 mg; 72%).

Anal: (C <sub>28</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub> )				
Calc.	C, 57.56;	H, 8.01;	N, 9.20	0.3 EtOAc,
Found	C, 57.41;	H, 7.98;	N, 9.20	

TLC: R<sub>f</sub> 0.26 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

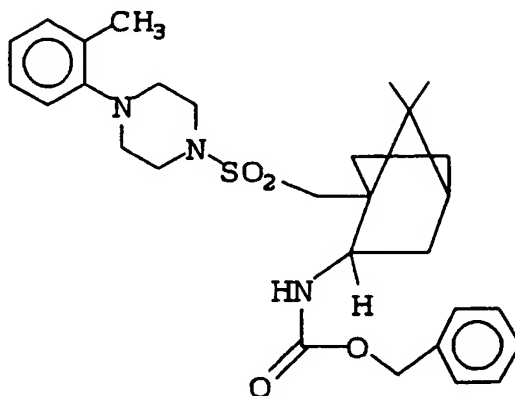
HPLC (method A): retention time 9.10 min

FAB MS: m/z 583 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.62 (br s, 1H), 7.18 (m, 2H), 7.02 (m, 2H), 4.37 (m, 1H), 2.92 (s, 3H), 2.36 (s, 6H), 2.30 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H)

## EXAMPLE 39

1-((7,7-DIMETHYL-2-ENDO-BENZYLOXYCARBONYLAMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



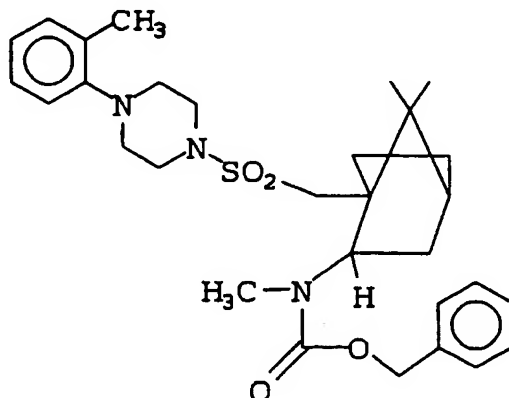
To a 0°C stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.20 g; 3.07 mmol) in CHCl<sub>3</sub> (100 mL) was added DIEA (0.80 mL; 4.6 mmol) and benzyl chloroformate (0.58 g; 3.4 mmol). The solution was stirred at 0°C for 1 h and then at ambient temperature for 4 h. The reaction mixture was washed with 5% aqueous HCl (2 x 50 mL) and aqueous NaHCO<sub>3</sub> (100 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc-hexanes as eluant. The title compound was obtained as a white foam. (1.45 g; 90%).

Anal: (C <sub>29</sub> H <sub>39</sub> N <sub>3</sub> O <sub>4</sub> S)					
Calc.	C, 65.75;	H, 7.53;	N, 7.77	0.15 EtOAc,	0.1 H <sub>2</sub> O
Found	C, 65.90;	H, 7.49;	N, 7.80		

TLC: R<sub>f</sub> 0.38 (1:3 EtOAc:hexanes)  
HPLC (method A): retention time 12.18 min  
FAB MS: m/z 526 (M<sup>+</sup> + H)

## EXAMPLE 40

1-((7,7-DIMETHYL-2-ENDO-METHYL(BENZYLOXYCARBONYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a 0°C stirred solution of 1-((7,7-dimethyl-2-endo-benzyloxycarbonylamino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.46 g; 2.78 mmol) in DMF (20 mL) was added iodomethane (0.435 mL; 7.00 mmol) and sodium hydride (0.139 mg of a 60% dispersion in mineral oil; 3.48 mmol). The solution was stirred at 0°C for 1 h and then at ambient temperature for 18 h. The reaction mixture was treated with HOAc (1 mL) and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with aqueous NaHCO<sub>3</sub> (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:5 EtOAc-hexanes as eluant. The title compound was obtained as a white foam. (1.40 g; 93%).

Anal: (C <sub>30</sub> H <sub>41</sub> N <sub>3</sub> O <sub>4</sub> S)				
Calc.	C, 66.03;	H, 7.70;	N, 7.70	0.33 H <sub>2</sub> O
Found	C, 66.03;	H, 7.63;	N, 7.68	

TLC: R<sub>f</sub> 0.44 (1:4 EtOAc:hexanes)

HPLC (method A): retention time 12.86 min

FAB MS: m/z 540 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.25-7.45 (m, 5H), 7.20 (m, 2H), 7.02 (m, 2H), 5.11 (AB quartet, 2H), 4.83 (m, 1H), 3.03 (s, 3H), 2.32 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H)

#### EXAMPLE 41

#### 1-((7,7-DIMETHYL-2-ENDO-METHYL(2S-AMINO-4-(METHYLSULFONYL)BUTANOYL)AMINO-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred, argon purged solution of 1-((7,7-dimethyl-2-endo-methyl(benzyloxycarbonyl)amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.1 g; 2.0 mmol) in 96:4 MeOH-HCO<sub>2</sub>H (25 mL) was added palladium black (0.4 g). The reaction mixture was stirred for 16 h at ambient temperature. The catalyst was removed by filtration through Celite, and the filtrate solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The product, 1-((7,7-dimethyl-2-endo-methylamino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, was obtained as a white foam. (0.79 g; 95%). To a stirred solution of 1-((7,7-dimethyl-2-endo-methylamino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.700 g; 1.73 mmol) in CHCl<sub>3</sub> (60 mL) was added the acid fluoride of N<sup>ε</sup>-Fmoc-L-methionine sulfone (1.23 g; 3.03 mmol) and DIEA (0.52 mL; 3.0 mmol). The mixture was stirred at ambient temperature for 24 h, and then extracted with 5% aqueous HCl (30 mL), water (30 mL), and aqueous NaHCO<sub>3</sub> (2 x 30 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in DMF (10 mL), and to the solution was added diethylamine (2 mL). The mixture was stirred at ambient temperature for 6 h. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The title compound was obtained as a foam from CHCl<sub>3</sub>-ether (0.71 g; 61%).

Anal: (C <sub>27</sub> H <sub>44</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub> )					
Calc.	C, 56.26;	H, 7.80;	N, 9.40	0.1 CHCl <sub>3</sub> ,	0.2 ether
Found	C, 56.21;	H, 7.79;	N, 9.22		

TLC: R<sub>f</sub> 0.10 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 9.01 min

FAB MS: m/z 569 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.18 (m, 2H), 7.03 (m, 2H), 5.20 (ddd, 1H), 3.95 (dd, J = 9.3, 4.1 Hz, 1H), 3.18 (s, 3H), 2.91 (s, 3H), 2.30 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H)

## EXAMPLE 42

1-((7,7-DIMETHYL-2-ENDO-METHYL(2S-DIMETHYLAMINO-4-(METHYLSULFONYL)BUTANOYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred solution of 1-((7,7-dimethyl-2-endo-methyl(2S-amino-4-(methylsulfonyl)butanoyl)amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (150 mg; 0.264 mmol) in 1:1 HOAc:MeOH (6 mL) was added 37% aqueous formaldehyde (1 mL) and NaBH<sub>3</sub>CN (30 mg; 0.47 mmol). The solution was stirred at ambient temperature for 4 h. Aqueous NaHCO<sub>3</sub> (1 mL) was added and the solvents were removed under reduced pressure. The residue was suspended in EtOAc (50 mL) and washed with water (2 x 25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: (C <sub>29</sub> H <sub>48</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub> )					
Calc.	C, 44.88;	H, 5.94;	N, 6.16	2.5 TFA,	1.5 H <sub>2</sub> O
Found	C, 44.80;	H, 5.94;	N, 6.18		

TLC: R<sub>f</sub> 0.45 (95:5:0.5 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)  
 HPLC (method A): retention time 9.04 min  
 FAB MS: m/z 597 (M<sup>+</sup> + H)  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.2-7.3 (m, 4H), 5.15 (m, 1H), 4.79 (br t, 1H), 3.21 (s, 3H), 2.98 (s, 3H), 2.95 (s, 6H), 2.43 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H)

## EXAMPLE 43

1-((7,7-DIMETHYL-2-ENDO-(4-IMIDAZOLYL)ACETYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.84 mmol) in DMF (30 mL) was added 4-imidazole acetic acid hydrochloride (0.938 g; 5.76 mmol), BOP (2.13 g; 4.80 mmol), and DIEA (2.61 mL; 15.0 mmol). The reaction mixture was stirred for 24 h at ambient temperature, and the solvent was removed under reduced pressure. The residue was suspended in EtOAc (100 mL) and filtered through Celite to remove red polymer. The filtrate was washed with aqueous NaHCO<sub>3</sub> (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 92:8:0.8 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH as eluant. The title compound was obtained as white foam.

FAB MS: m/z 500 (M<sup>+</sup> + H)

## EXAMPLE 44

1-((7,7-DIMETHYL-2-ENDO-(2-(4-IMIDAZOLYL)PROPANOYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINE

To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.1 g; 2.8 mmol) in DMF (25 mL) was added 2-(1-benzyloxymethyl-5-imidazolyl)propionic acid hydrochloride (0.920 g; 3.10 mmol), BOP (1.35 g; 3.05 mmol), and DIEA (1.50 mL; 8.61 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and more DIEA (ca. 0.2 mL) was added to bring the mixture to pH 8. After another 1 h, the solvent was removed under reduced pressure. The residue was dissolved in CHCl<sub>3</sub> (150 mL) and washed with aqueous NaHCO<sub>3</sub> (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure to give a solid. Recrystallization from EtOAc gave crystals (0.51 g) which, by <sup>1</sup>H NMR analysis, proved to be a 90:10 mixture of isomers (product A). The filtrate was purified by pressurized silica gel column chromatography using 95:5 CHCl<sub>3</sub>:MeOH as eluant, giving a white foam (1.0 g). <sup>1</sup>H NMR indicated this material to be a 1:2 mixture of isomers (product B). Products A and B were individually deblocked by hydrogenation for 24 h at ambient temperature in 3:1 MeOH:HOAc using 25 weight% palladium black under

1 atmosphere of hydrogen. The catalyst was removed by filtration through Celite and the solvents were removed under reduced pressure. The catalyst was removed by filtration through Celite, and the filtrate solvents were removed under reduced pressure. The residue derived from product A was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The TFA salt of the title compound (90:10 mixture by  $^1\text{H}$  NMR) was obtained as a lyophilized powder. Product B was purified by pressurized silica gel column chromatography using 95:5:0.5  $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$  as eluant. The title compound was obtained as white foam from  $\text{CHCl}_3$ -ether (1:2 mixture by  $^1\text{H}$  NMR). The two isomers had identical chromatographic behavior.

Anal: ( $\text{C}_{27}\text{H}_{37}\text{N}_5\text{O}_3\text{S}$ )					
Calc.	C, 60.36;	H, 7.49;	N, 12.46	0.25 $\text{CHCl}_3$ ,	0.25 ether
Found	C, 60.49;	H, 7.26;	N, 12.48		

TLC:  $R_f$  0.30 (93:7:0.7  $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$ )

HPLC (method A): retention time 8.79 min

FAB MS:  $m/z$  514 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.75 (br s, 1H), 7.20 (m, 2H), 7.0 (m, 3H), 4.40 (m, 1H), 2.30, 2.29 (two singlets, ca. 2:1 ratio, 3H), 1.57, 1.53 (two doublets,  $J = 7$  Hz, ca. 2:1 ratio, 3H), 1.00 (s, 3H), 0.96 (s, 3H)

L-369,076

Anal: ( $\text{C}_{27}\text{H}_{37}\text{N}_5\text{O}_3\text{S}$ )				
Calc.	C, 48.91;	H, 5.36;	N, 9.03	2.3 TFA
Found	C, 48.99;	H, 5.21;	N, 9.03	

TLC:  $R_f$  0.30 (93:7:0.7  $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$ )

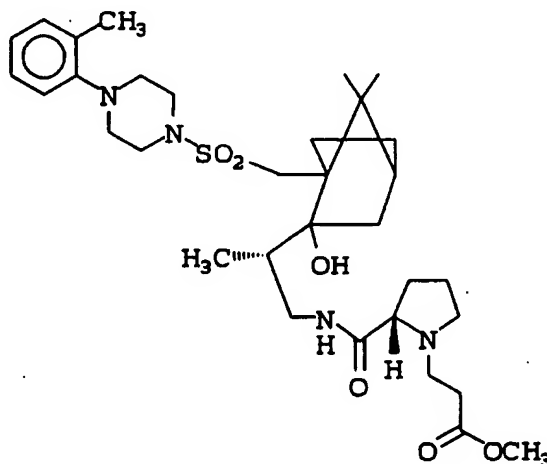
HPLC (method A): retention time 8.79 min

FAB MS:  $m/z$  514 ( $\text{M}^+ + \text{H}$ )

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.43 (s, 1H), 7.70 (d, 1H), 7.25 (m, 2H), 7.20 (s, 1H), 7.15 (m, 2H), 4.40 (m, 1H), 4.03 (q,  $J = 7$  Hz, 1H), 2.38 (s, 3H), 1.57 (d,  $J = 7$  Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H)

#### EXAMPLE 45

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(METHOXYCARBONYLETHYL)PROLYL)AMINO)-PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE





To a stirred solution of 1-((7,7-dimethyl-2- $\alpha$ -hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl-(2.2.1)-bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 2.74 mmol) in methanol (15 mL) was added methyl acrylate (0.310 mL; 3.43 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>33</sub> H <sub>52</sub> N <sub>4</sub> O <sub>6</sub> S)				
Calc.	C, 53.10;	H, 6.59;	N, 6.82	1.65 TFA
Found	C, 53.09;	H, 6.58;	N, 6.88	

TLC: R<sub>f</sub> 0.55 (95:5 CHCl<sub>3</sub>:MeOH)

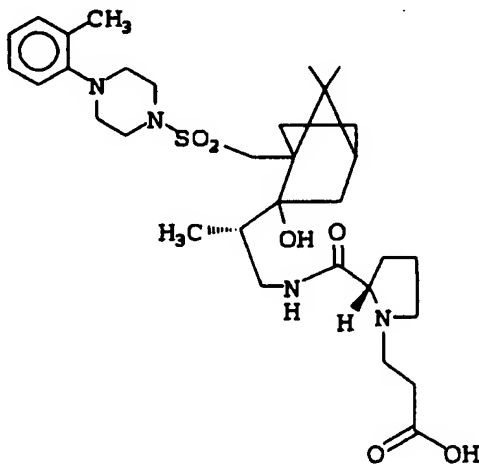
HPLC (method A): retention time 9.45 min

FAB MS: m/z 633 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.18 (m, 2H), 7.03 (m, 2H), 4.55 (m, 1H), 3.72 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.01 (d, J=6 Hz, 3H)

#### EXAMPLE 46

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(CARBOXYETHYL)PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2- $\alpha$ -hydroxy-2-endo-2-(1-(L-N-(methoxycarbonyl)ethyl)prolyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.00 g; FW = 821; 1.22 mmol) in THF (15 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>32</sub> H <sub>50</sub> N <sub>4</sub> O <sub>6</sub> S)				
Calc.	C, 51.88;	H, 6.34;	N, 6.80	1.8 TFA
Found	C, 51.87;	H, 6.28;	N, 6.82	

TLC: R<sub>f</sub> 0.40 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 8.88 min

FAB MS:  $m/z$  619 ( $M^+ + H$ )

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.50 (br s, 1H), 7.20 (m, 2H), 7.05 (m, 2H), 2.33 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.99 (d,  $J = 6$  Hz, 3H)

#### 5 EXAMPLE 47

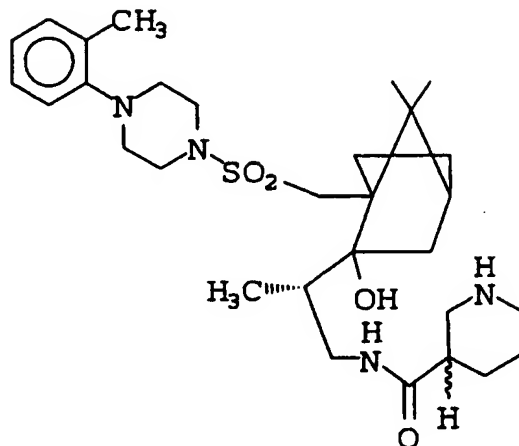
1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE

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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (2.50 g; 5.57 mmol) in DMF (35 mL) was added N-Fmoc-piperidine-3-carboxylic acid (2.15 g; 6.13 mmol), BOP (2.75 g; 6.20 mmol), and DIEA (2.16 mL; 12.4 mmol). After 16 h, diethylamine (6 mL) was added and the solution was stirred at ambient temperature for 4 h. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc (150 mL) and washed with aqueous  $NaHCO_3$  (2 x 75 mL) and water (2 x 75 mL). The organic phase was dried ( $MgSO_4$ ), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 93:7:0.7  $CHCl_3$ :MeOH: $NH_4OH$  as eluant. The title compound (1:1 mixture of diastereomers) was obtained as a white foam.

40

Anal: ( $C_{30}H_{48}N_4O_4S$ )				
Calc.	C, 56.37;	H, 7.49;	N, 8.54	0.8 $CHCl_3$
Found	C, 56.49;	H, 7.44;	N, 8.50	

TLC:  $R_f$  0.40 (90:10:1  $CHCl_3$ :MeOH: $NH_4OH$ )

HPLC (method A): retention time 8.67 min

FAB MS:  $m/z$  561 ( $M^+ + H$ )

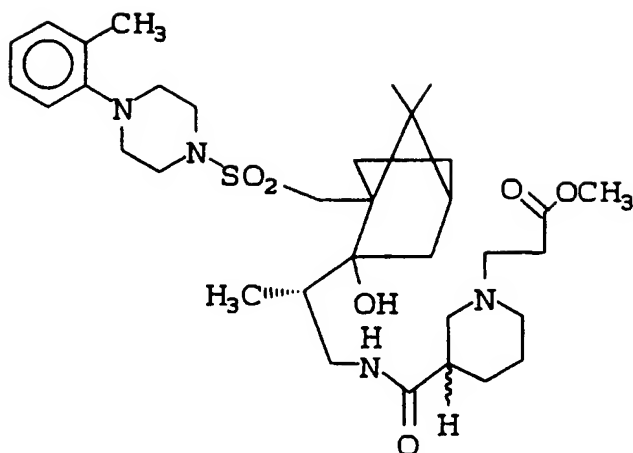
$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.50 (br s, 1H), 7.20 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.17 (s, 3H), 1.00-1.04 (overlapping singlet and doublet, 6H)

50

#### EXAMPLE 48

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-METHOXYCARBONYLETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE

55



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.50 g; 0.89 mmol) in methanol (10 mL) was added methyl acrylate (0.120 mL; 1.34 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

Anal: (C <sub>34</sub> H <sub>54</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc.	C, 55.40;	H, 7.06;	N, 7.08	1.25 TFA,	0.1 H <sub>2</sub> O
Found	C, 55.39;	H, 7.05;	N, 7.03		

TLC: R<sub>f</sub> 0.35 (95:5 CHCl<sub>3</sub>:MeOH)

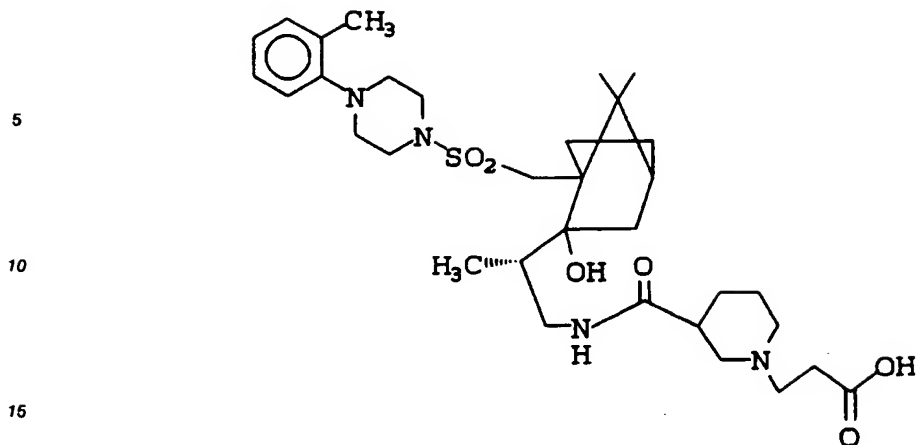
HPLC (method A): retention time 10.71 min

FAB MS: m/z 647 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.02 (m, 2H), 3.72, 3.69 (two singlets, 3H), 2.32, 2.31 (two singlets, 3H), 1.16, 1.15 (two singlets, 3H), 0.98-1.04 (two coincident singlets and two overlapping doublets, 6H)

#### EXAMPLE 49

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-CARBOXYETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



20 To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.30 g; 0.46 mmol) in THF (10 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

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Anal: (C <sub>33</sub> H <sub>52</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc. C,	51.59;	H, 6.44;	N, 6.54	1.9 TFA,	0.4 H <sub>2</sub> O
Found C,	51.60;	H, 6.44;	N, 6.83		

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TLC: R<sub>f</sub> 0.15 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 10.27 min

FAB MS: m/z 633 (M<sup>+</sup> + H)

35 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 2H), 7.05 (m, 2H), 2.39, 2.32 (two singlets, 3H), 1.12, 1.11 (two singlets, 3H), 0.95-1.03 (two coincident singlets and two overlapping doublets, 6H)

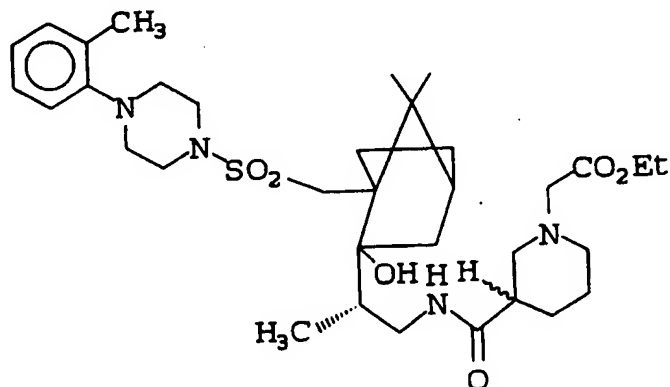
#### EXAMPLE 50

40 1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-ETHOXYCARBONYLMETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE

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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.50 g; 0.89 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.110 mL; 0.99 mmol) and DIEA (0.172 mL; 0.99 mmol). After 24 h at ambient temperature, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (50 mL) and washed with 5% aqueous citric acid (25 mL), water (25 mL), and aqueous NaHCO<sub>3</sub> (25 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered, and the solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 1:1 EtOAc:CHCl<sub>3</sub> as eluant. The title compound (1:1 mixture of diastereomers) was obtained as a white foam.

Anal: (C<sub>34</sub>H<sub>54</sub>N<sub>4</sub>O<sub>6</sub>S)

Calc.	C, 58.66;	H, 7.77;	N, 7.93	0.5 CHCl <sub>3</sub>
Found	C, 58.87;	H, 7.83;	N, 7.88	

TLC: R<sub>f</sub> 0.28 (1:1 CHCl<sub>3</sub>:EtOAc)

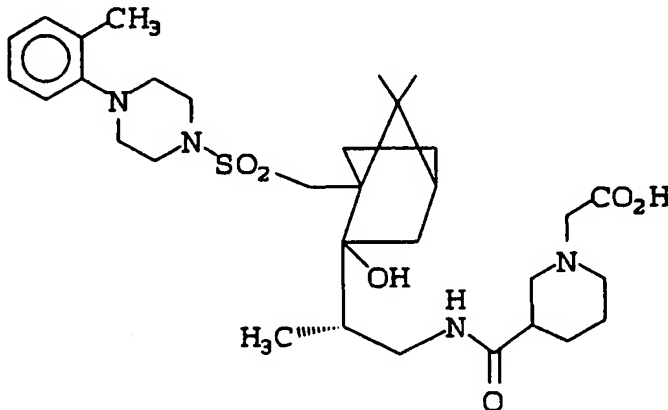
HPLC (method A): retention time 9.76 min

FAB MS: m/z 647 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.2 (very br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 4.20 (two very closely spaced quartets, 2H), 2.30, 2.31 (two singlets, 3H), 1.28 (t, J = 7 Hz, 3H), 1.07, 1.08 (two singlets, 3H), 1.03-1.08 (two coincident singlets and two overlapping doublets, 6H)

#### EXAMPLE 51

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-CARBOXYMETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.360 g; 0.555 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was made acidic by the addition of HOAc (1 mL) and evaporated under reduced pressure. The residue was suspended in CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was evaporated under reduced pressure several times from CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (1:1 mixture of diastereomers) as a white foam.

Anal: (C<sub>32</sub>H<sub>50</sub>N<sub>4</sub>O<sub>6</sub>S)

Calc. C,	58.27;	H, 7.62;	N, 7.99	1.0 NaOAc
Found C,	58.47;	H, 7.71;	N, 7.90	

TLC: R<sub>f</sub> 0.55 (85:15 CHCl<sub>3</sub>:MeOH)

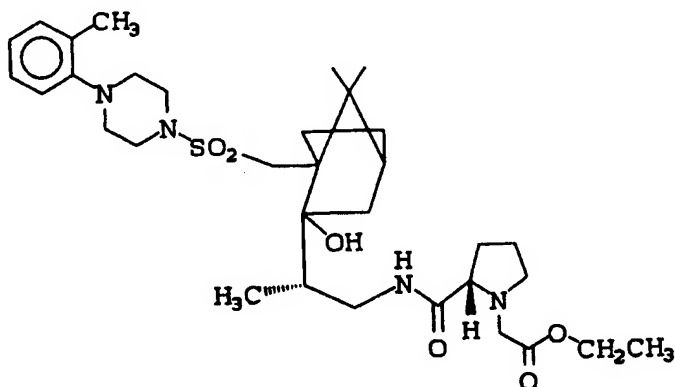
HPLC (method A): retention time 8.77 min

FAB MS:  $m/z$  619 ( $M^+ + H$ )

$^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  7.15 (m, 2H), 7.05 (d,  $J=7.3$  Hz, 1H), 6.96 (t,  $J=7.3$  Hz, 1H), 2.31 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.98 (d,  $J=6$  Hz, 3H)

# 5 EXAMPLE 52

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(ETHOXYCARBOXYMETHYL)PROLYL)AMINO)-  
PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE



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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl-(2.2.1)-bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.37 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.045 mL; 0.40 mmol) and DIEA (0.071 mL; 0.41 mmol). After 24 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

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Anal: (C <sub>33</sub> H <sub>52</sub> N <sub>4</sub> O <sub>6</sub> S)				
Calc.	C, 54.25;	H, 6.79;	N, 7.07	1.4 TFA
Found	C, 54.25;	H, 6.78;	N, 7.02	

TLC:  $R_f$  0.50 (1:1 EtOAc:CHCl<sub>3</sub>)

HPLC (method A): retention time 9.68 min

FAB MS:  $m/z$  633 ( $M^+ + H$ )

$^1H$  NMR (400 MHz,  $CD_3OD$ ):  $\delta$  7.17 (m, 2H), 7.06 (d,  $J=6$  Hz, 1H), 6.98 (t,  $J=6$  Hz, 1H), 4.25 (m, 3H), 4.08 (d,  $J=15$  Hz, 1H), 2.32 (s, 3H), 1.27 (t,  $J=7$  Hz, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 1.01 (d,  $J=6$  Hz, 3H)

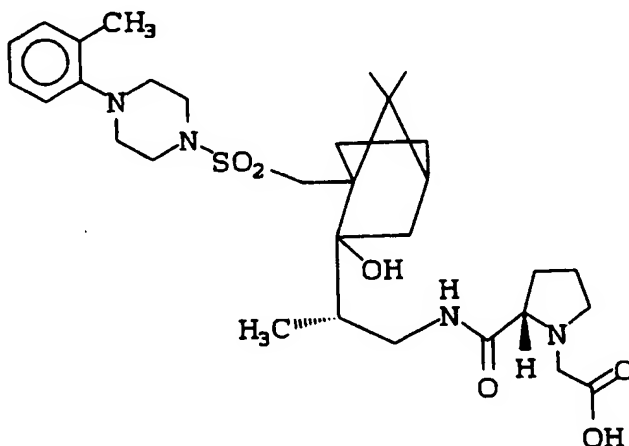
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## EXAMPLE 53

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(CARBOXYMETHYL)PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-(N-ethoxycarbonylmethyl)prolyl)-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.32 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C<sub>31</sub>H<sub>48</sub>N<sub>4</sub>O<sub>6</sub>S)

Calc.	C, 52.64;	H, 6.43;	N, 7.22	1.5 TFA
Found	C, 52.49;	H, 6.51;	N, 7.22	

TLC: R<sub>f</sub> 0.40 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 8.79 min

FAB MS: m/z 605 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.17 (m, 2H), 7.07 (d J=5 Hz, 1H), 6.99 (t, J=5 Hz, 1H), 4.30 (dd, J=4, 5 Hz, 1H), 4.21 (d, J=14 Hz, 1H), 4.04 (d, J=14 Hz, 1H), 2.32 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 1.01 (d, J=7 Hz, 3H)

## EXAMPLE 54

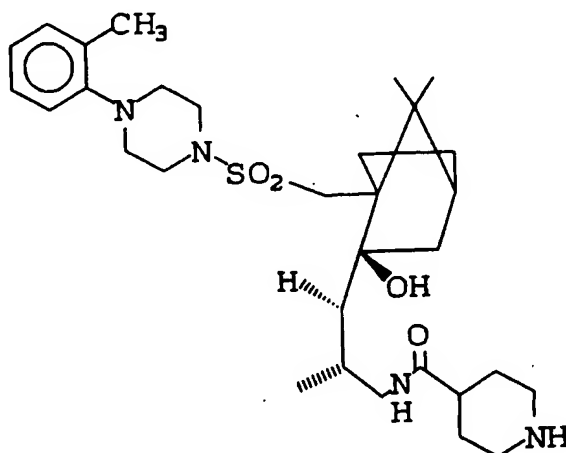
1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE

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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.34 mmol) in DMF (20 mL) was added N-Fmoc-piperidine-4-carboxylic acid (1.29 g; 3.67 mmol), BOP (1.64 g; 3.70 mmol), and DIEA (1.28 mL; 7.34 mmol). After 16 h, diethylamine (5 mL) was added and the solution was stirred at ambient temperature for 4 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

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Anal: (C <sub>30</sub> H <sub>48</sub> N <sub>4</sub> O <sub>4</sub> S)					
Calc.	C, 51.93;	H, 6.43;	N, 7.15	1.95 TFA,	0.05 H <sub>2</sub> O
Found	C, 51.93;	H, 6.36;	N, 7.28		

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TLC: R<sub>f</sub> 0.15 (90:10:1 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

HPLC (method A): retention time 8.33 min

FAB MS: m/z 561 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (m, 3H), 7.08 (m, 2H), 2.33 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 1.00 (d, J=6 Hz, 3H)

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## EXAMPLE 55

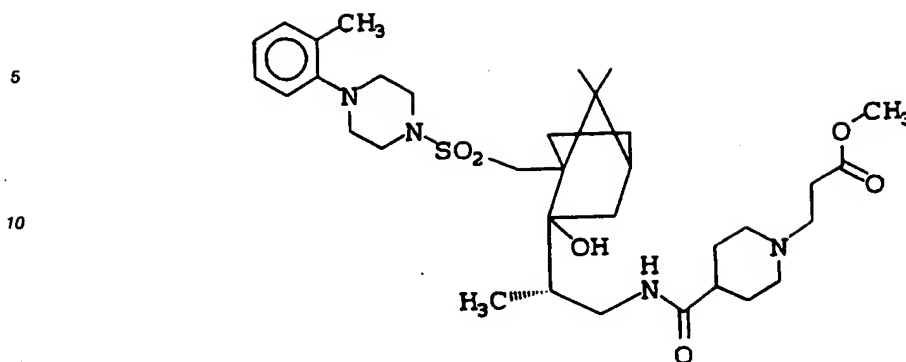
1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-METHOXYCARBONYLETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE

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To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(4-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.30 g; 0.53 mmol) in methanol (5 mL) was added methyl acrylate (0.072 mL; 0.80 mmol). After 48 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

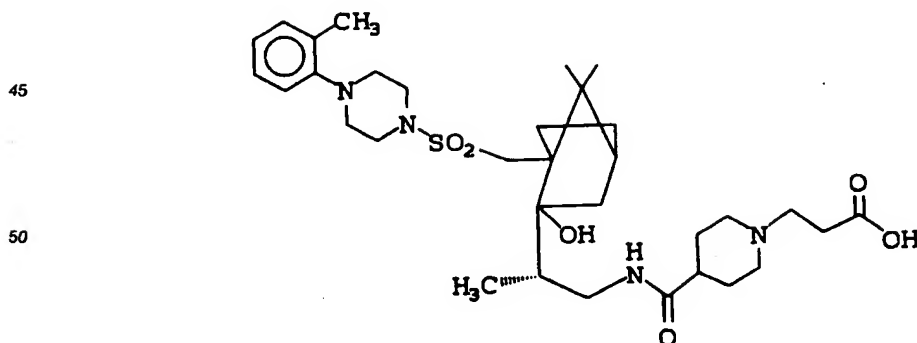
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Anal: (C <sub>34</sub> H <sub>54</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc.	C, 53.04;	H, 6.65;	N, 6.60	1.75 TFA,	0.15 H <sub>2</sub> O
Found	C, 53.05;	H, 6.62;	N, 6.69		

TLC: R<sub>f</sub> 0.25 (95:5 CHCl<sub>3</sub>:MeOH)  
 HPLC (method A): retention time 9.02 min  
 FAB MS: m/z 647 (M<sup>+</sup> + H)  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.45 (br t, 1H), 7.21 (m, 2H), 7.09 (m, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 1.15 (s, 3H), 1.00-1.02 (overlapping s and d, 6H)

### 35 EXAMPLE 56

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-CARBOXYETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.15 g; 0.23 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The

solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>33</sub> H <sub>52</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc.	C, 53.09;	H, 6.65;	N, 6.84	1.6 TFA,	0.2 H <sub>2</sub> O
Found	C, 53.08;	H, 6.66;	N, 6.85		

TLC: R<sub>f</sub> 0.10 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

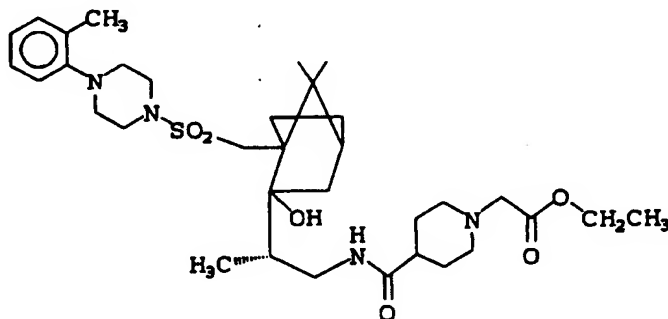
HPLC (method A): retention time 8.72 min

FAB MS: m/z 633 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.38 (br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.29 (s, 3H), 1.13 (s, 3H), 0.98-1.01 (overlapping s and d, 6H)

#### EXAMPLE 57

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-ETHOXYCARBONYLMETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-piperidinyldicarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.36 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.044 mL; 0.40 mmol) and DIEA (0.070 mL; 0.40 mmol). After 24 h at ambient temperature, the solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>34</sub> H <sub>54</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc.	C, 52.81;	H, 6.67;	N, 6.57	1.75 TFA,	0.35 H <sub>2</sub> O
Found	C, 52.80;	H, 6.64;	N, 6.69		

TLC: R<sub>f</sub> 0.35 (95:5 CHCl<sub>3</sub>:MeOH)

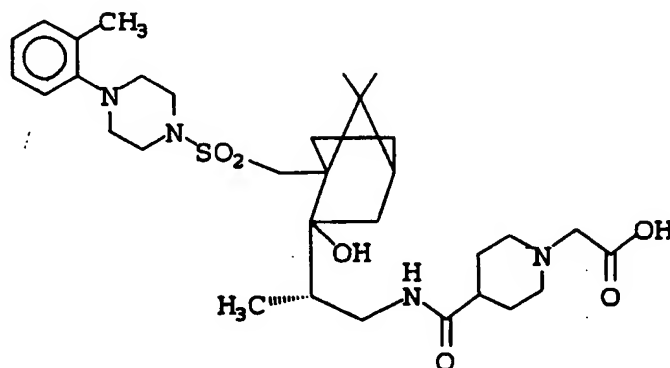
HPLC (method A): retention time 9.26 min

FAB MS: m/z 647 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 2H), 7.04 (m, 2H), 4.26 (q, J = 7 Hz, 2H), 3.85 (s, 2H), 2.32 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.14 (s, 3H), 1.02-1.05 (overlapping s and d, 6H)

## EXAMPLE 58

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-CARBOXYMETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO (2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl) methanesulfonyl)-4-(2-methylphenyl)piperazine (0.15 g; 0.23 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: (C <sub>32</sub> H <sub>50</sub> N <sub>4</sub> O <sub>6</sub> S)					
Calc.	C, 53.23;	H, 6.82;	N, 7.18	1.3 TFA,	0.75 H <sub>2</sub> O
Found	C, 53.20;	H, 6.81;	N, 7.18		

TLC: R<sub>f</sub> 0.15 (80:20:2 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH)

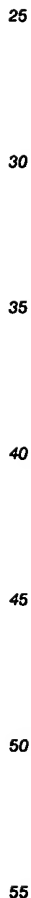
HPLC (method A): retention time 8.59 min

FAB MS: m/z 619 (M<sup>+</sup> + H)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.35 (br s, 1H), 7.17 (m, 2H), 7.02 (m, 2H), 3.90 (s, 2H), 2.30 (s, 2H), 1.13 (s, 3H), 1.01 (s, 3H), 0.97 (d, J = 6 Hz, 3H)

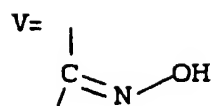
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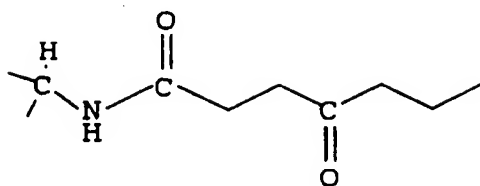


**TABLE**

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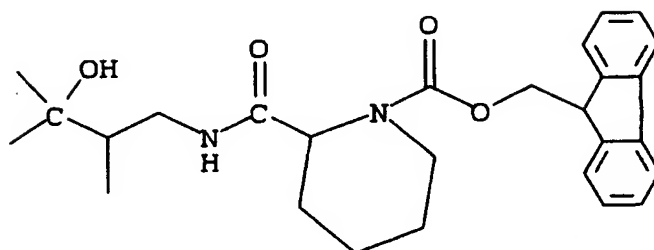


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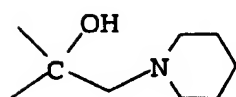
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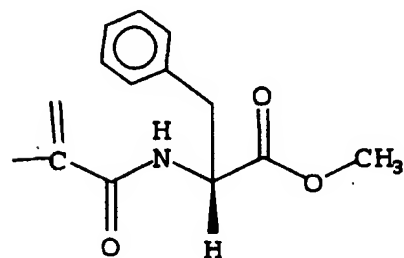
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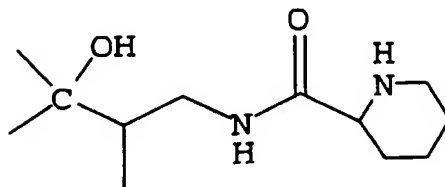
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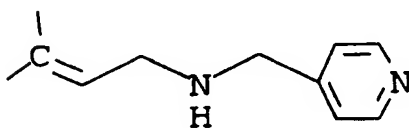
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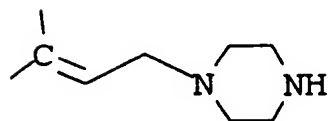
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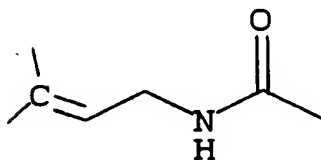
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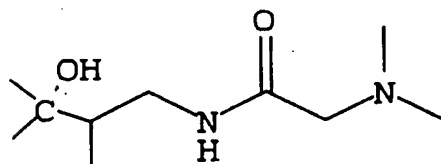
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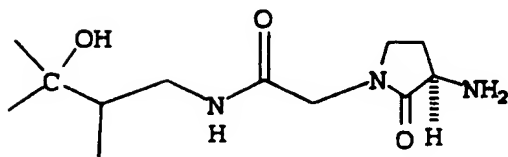
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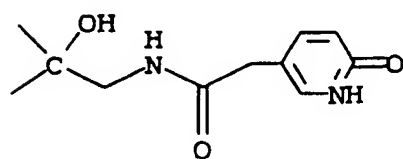
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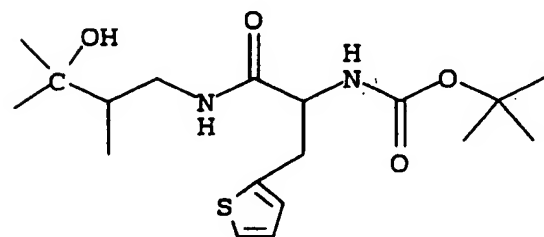
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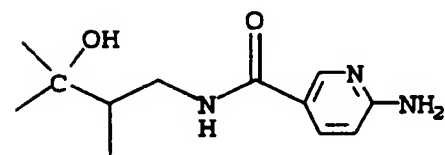
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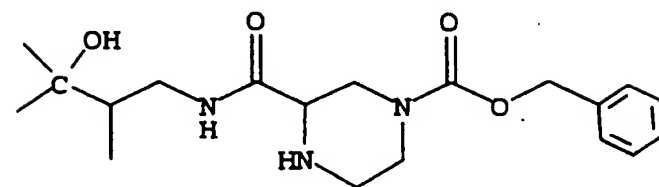
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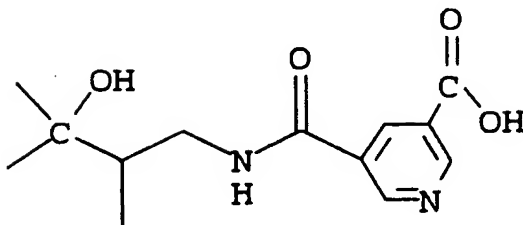
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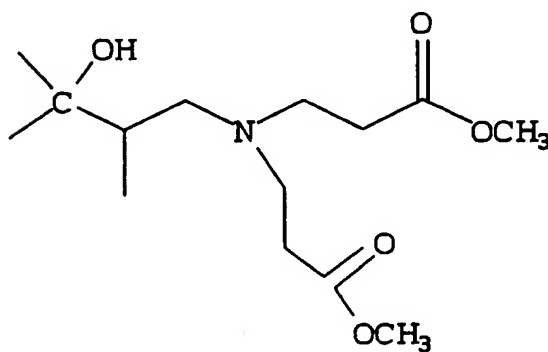
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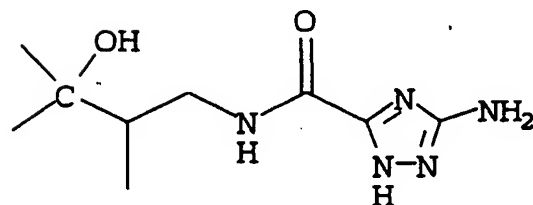
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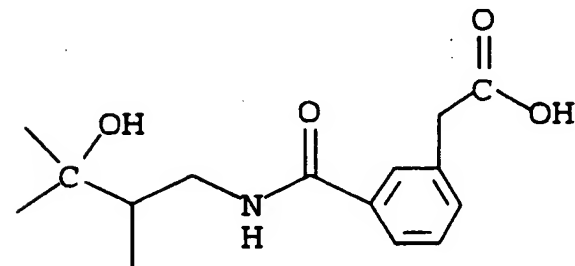
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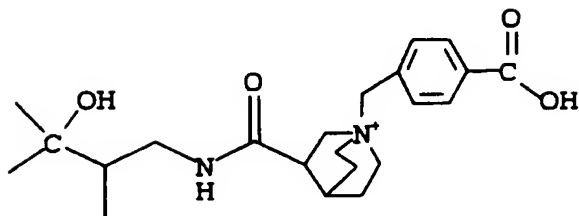
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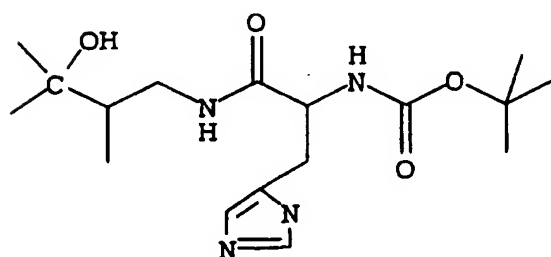
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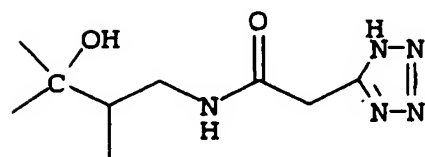
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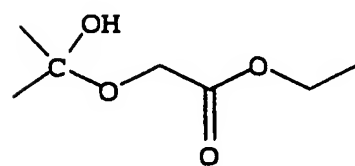
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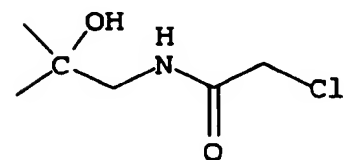
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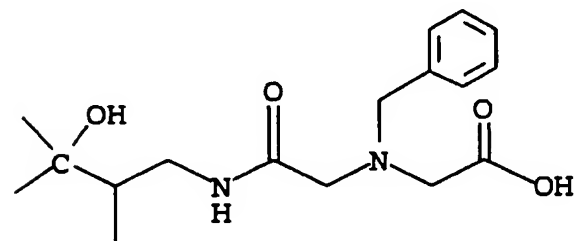
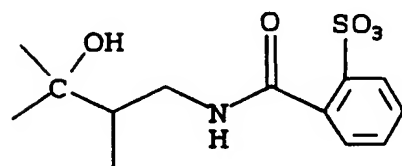
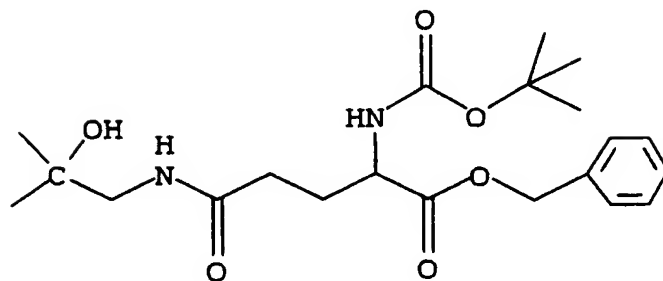
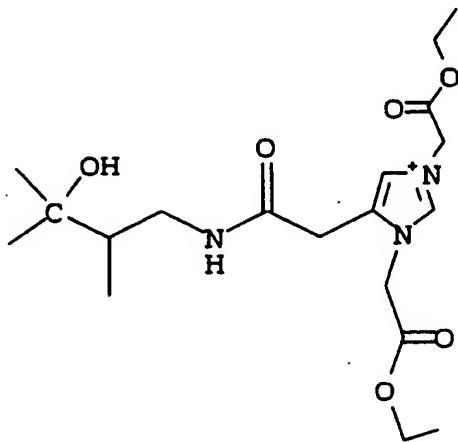
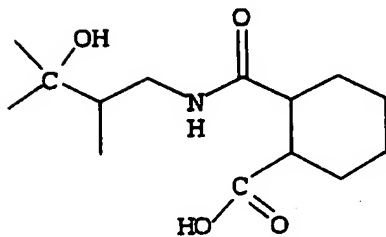


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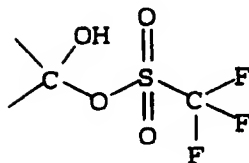
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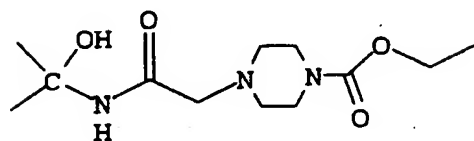


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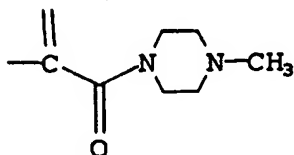


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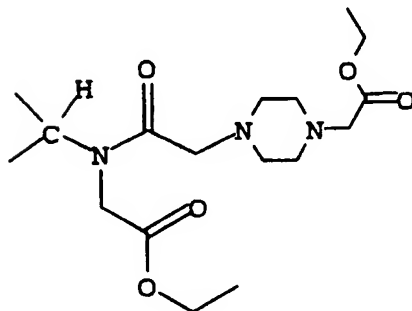
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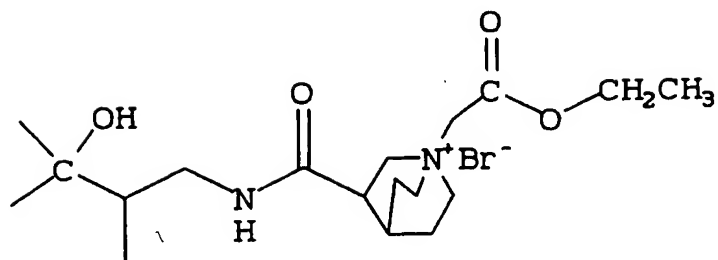
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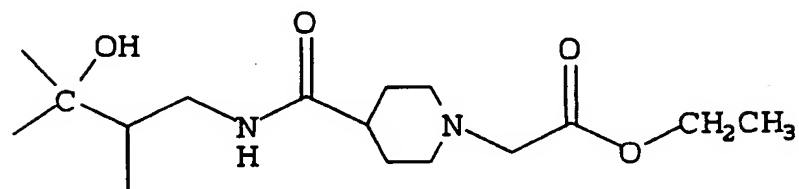
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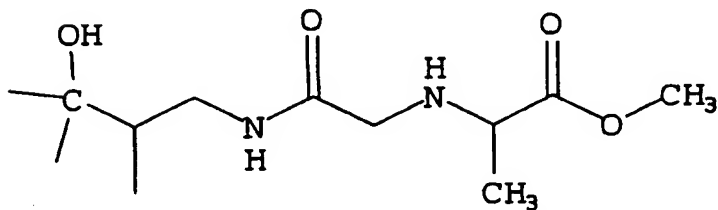
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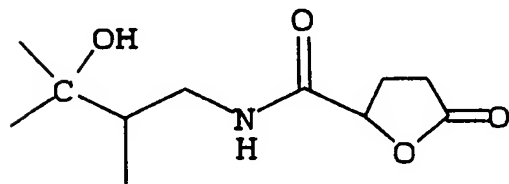
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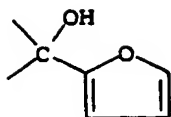


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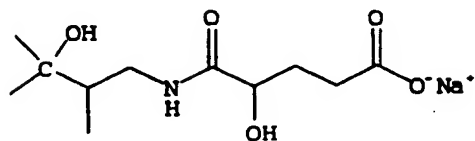
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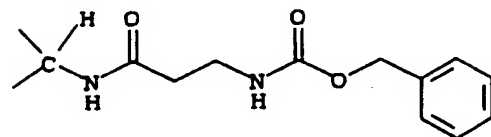
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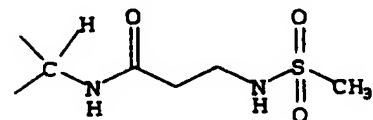
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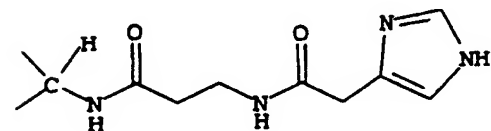
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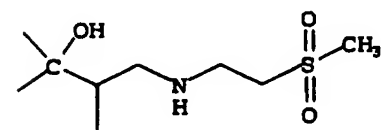
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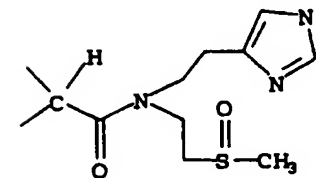
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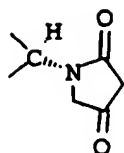
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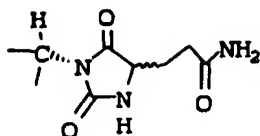
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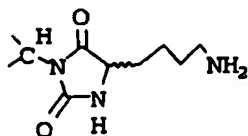
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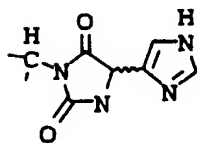
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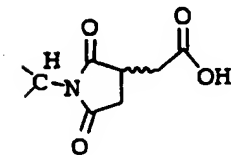
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Additional examples of species covered by this invention include the following non-limiting list:

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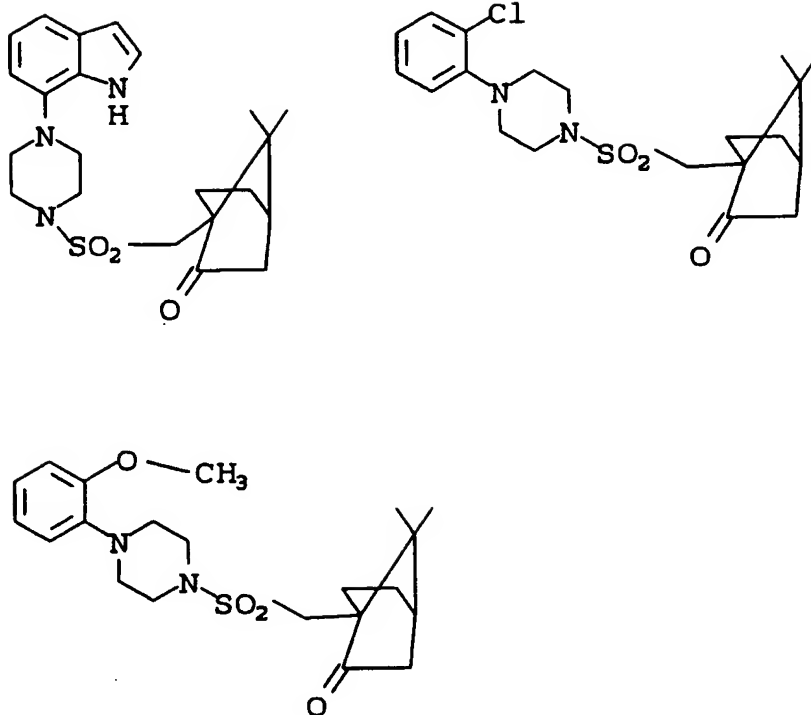
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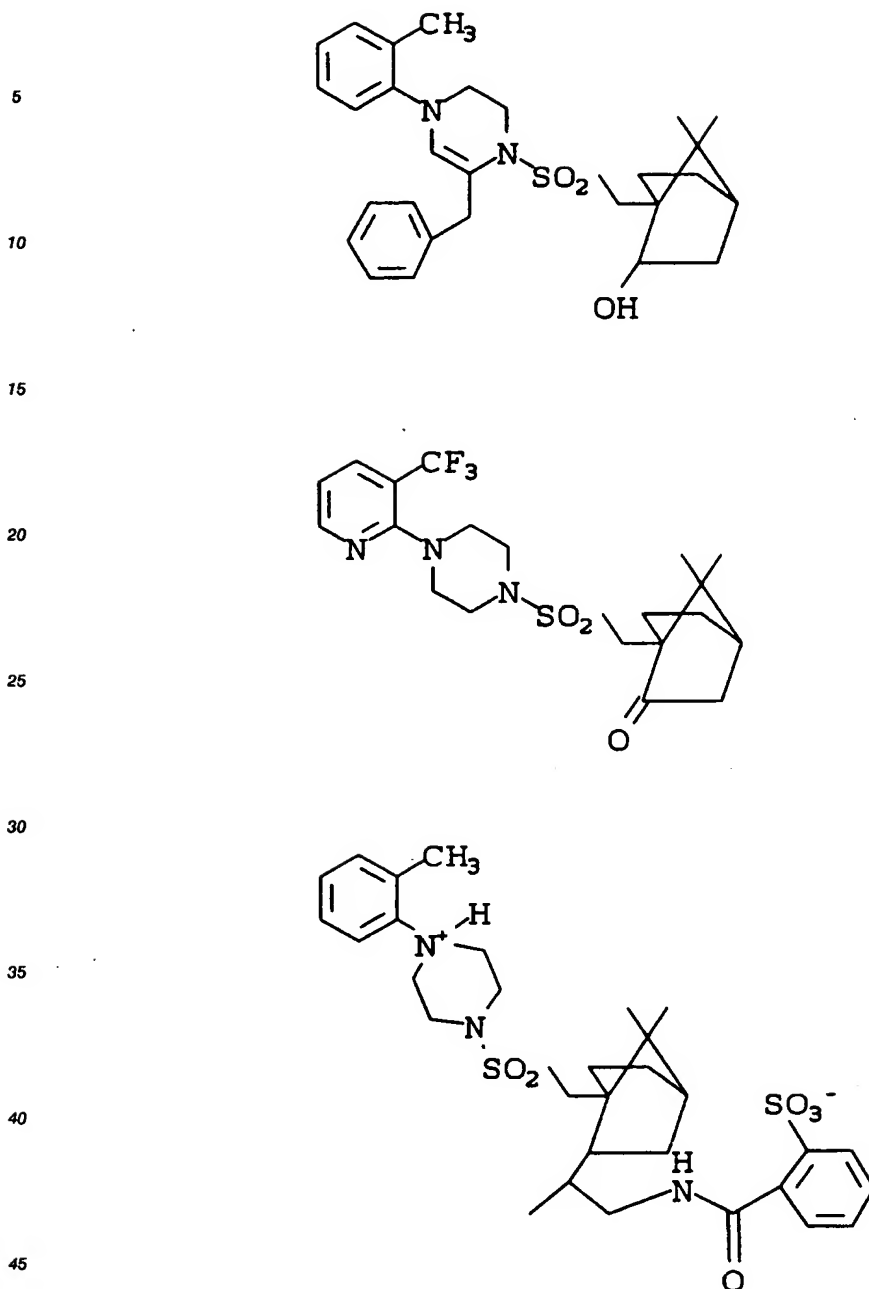
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### 50 EXAMPLE 33

#### RADIOGLAND BINDING ASSAYS

55 The high affinity binding of [<sup>3</sup>H] Oxytocin (OT) ([tyrosyl, 3,5-<sup>3</sup>H]OT; 30-60 Ci/mmol; New England Nuclear, Boston, MA) to uterine OT receptors was based on an assay\* using a crude membrane preparation of uteri taken from diethylstilbestrol dipropionate (DES)-treated (0.3 mg/kg, ip; 18-24) rats. Competition

\* Fuchs, A-R; Fuchs, F; Soloff, MS. 1985 J. Clin. Endocrinol. Metab. 60:37.

studies were conducted at equilibrium (60 minutes; 22°C) using 1 nM [<sup>3</sup>H]OT in the following assay buffer: 50 mM Tris-HCl, 5 mM MgCl<sub>2</sub>, and 0.1% BSA, pH 7.4. Nonspecific binding (10% of the total binding) was determined using 1 μM unlabeled OT and the binding reaction was terminated by filtration through glass fiber filters using a cell harvester (model 7019, Skatron, Inc., Sterling, VA). IC<sub>50</sub> (the concentration of tested compound that inhibits 50% of OT) was reported, unless otherwise noted.

The measurement of [<sup>3</sup>H]Vasopressin (AVP) ([phenylalanyl-3,4,5-<sup>3</sup>H]AVP; 80-90 Ci/mmol; New England Nuclear) binding to a crude membrane preparation of male rat liver (AVP-V<sub>1</sub> sites) or kidney medulla (AVP-V<sub>2</sub> sites) was determined according to the method of Butlen, et al. Competition assays were conducted at equilibrium (30 minutes at 30°C) using 1 nM [<sup>3</sup>H]AVP (liver) or 2 nM [<sup>3</sup>H]AVP (kidney) in the following assay buffer: 100 mM Tris-HCl, 5 mM MgCl<sub>2</sub>, 0.1% BSA, 50 μM phenylmethylsulfonylfluoride, and 50 μg/ml bacitracin, pH 8.0. Nonspecific binding (5-10% of the total binding) was determined using 10 μM unlabeled AVP, and the binding reaction was terminated by filtration as described above for the [<sup>3</sup>H]OT binding assay.

K<sub>i</sub> values were obtained for each compound from three to six separate determinations of the IC<sub>50</sub> values ( $K_i = IC_{50}/(1 + c/K_d)$ ) using K<sub>d</sub> values obtained from saturation binding assay: [<sup>3</sup>H]OT (uterus), 0.7 nM; [<sup>3</sup>H]AVP (liver), 0.4 nM; [<sup>3</sup>H] (kidney), 1.4 nM.

### Example

### IC<sub>50</sub>

20	1	1,000 nM
	2	150 nM
	3	180 nM
25	4	34 nM
	5	100 nM
	6	10 nM
30	7	8 nM
	8	18 nM
	9	5 nM
	10	48% inhibition at 100 nM
35	11	54 nM
	12	23% inhibition at 100 nM

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55 \*\* Butlen, D; Guillon, G; Rajerison, R.M.; Jard, S; Sawyer, W.H.; Manning, M. 1978 Mol Pharmacol 14:1006.

\*\*\* Cheng, Y-C; Prusoff, W.H.; 1973 Biochem Pharmacol 22:3099

<u>Example</u>		IC <sub>50</sub>
	14	1,100 nM
5	15	44% inhibition at 1,000 nM
	16	64% inhibition at 1,000 nM
	17	36% inhibition at 100 nM
10	18	75% inhibition at 1,000 nM
	19	31% inhibition at 1,000 nM
	20	72% inhibition at 1,000 nM
	21	38% inhibition at 1,000 nM
15	22	78% inhibition at 1,000 nM
	23	120 nM
	24	260 nM
20	25	34% inhibition at 100 nM
	26	35 nM
	27	37% inhibition at 100 nM
25	28	35% inhibition at 100 nM
	29	78% inhibition at 1,000 nM
	30	16% inhibition at 10,000 nM
	31	5% inhibition at 10,000 nM
30	32	37% inhibition at 1,000 nM
	33	460 nM
	34	-
35	35	91% inhibition at 100 nM
	36	7.7 nM
	37	1.2 nM
	38	5.4 nM
40	39	54% inhibition at 1,000 nM
	40	35% inhibition at 1,000 nM
	41	6.3 nM
45	42	9.2 nM
	43	110 nM

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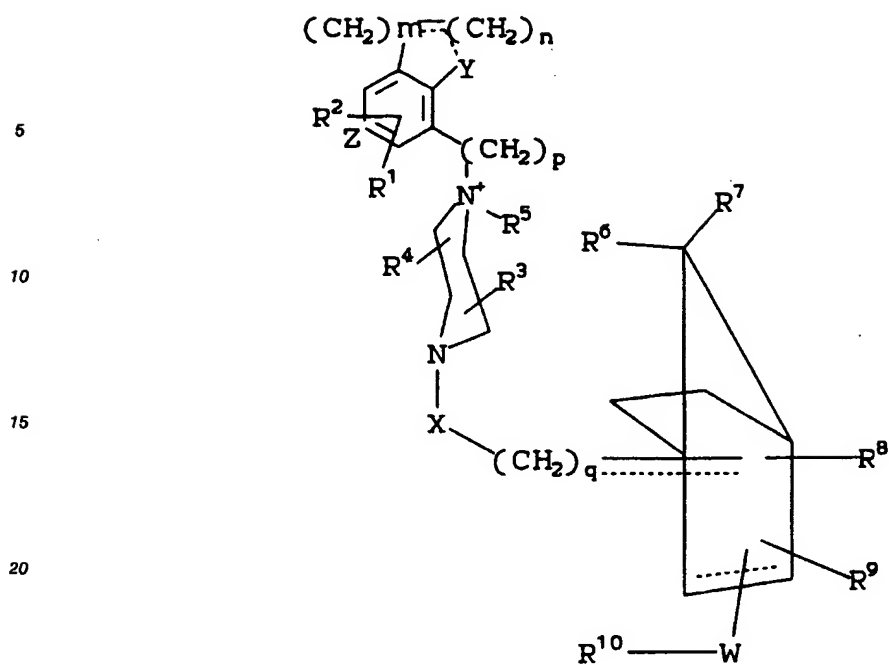
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	<u>Example</u>	<u>IC<sub>50</sub></u>
	44	26 nM
5		180 nM
	45	12 nM
	46	20 nM
	47	15 nM
10	48	30 nM
	49	25 nM
	50	66% inhibition at 100 nM
15	51	38 nM
	52	66% inhibition at 100 nM
	53	28 nM
	54	14 nM
20	55	30 nM
	56	54 nM
	57	66% inhibition at 100 nM
25	58	56 nM

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for prevention of preterm labor, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

#### Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

**W** is

an optional substituent that, when present, is substituted or unsubstituted alkyl where said substituent is carboxyl;

**X is**

(1) carbonyl or  
(2) sulfonyl;

**Y is**

(1) hydrogen,  
(2) alkyl or  
(3) NH;

**Z is**

(1) C or  
(2) N;

**R<sup>1</sup> and R<sup>2</sup> are independently one or more of**

(1) hydrogen,  
(2) halogen,  
(3) alkoxy or  
(4) alkylsulfonyl  
(5) unsubstituted or substituted alkyl wherein said substituent is;  
    amino  
    alkylamino, or  
    dialkylamino

**R<sup>3</sup> and R<sup>4</sup> are independently one or more of**

(1) hydrogen,  
(2) alkyl,  
(3) substituted alkyl where said substituent is  
amino  
alkylsulfonyl,  
arylsulfonyl,

alkylamino, or  
dialkylamino;  
(4) phenylalkyl or  
(5) oxo;

5  $R^5$  is

(1) hydrogen or  
(2) oxygen;

10  $R^6$  and  $R^7$  are independently one or more of

(1) hydrogen,  
(2) alkyl or  
3) joined to form unsubstituted or substituted  
cycloalkyl where said is substituent is  
hydroxy or  
15 hydroxyalkyl;

$R^8$  and  $R^9$  are independently one or more of

(1) hydrogen,  
(2) hydroxy,  
(3) oxo,  
20 (4) halogen,  
(5) oxime,  
(6) cyclic epoxide,  
(7) methylene,  
(8) carboxyl,  
25 (9) alkoxycarbonyl,  
(10) alkylcarbonyloxy,  
(11) alkoxycarbonylalkoxy,  
(12) sulfonyloxy,  
(13) trihaloalkylsulfonyloxy,  
30 (14) unsubstituted or substituted amino where  
said substituent is one or more of  
alkyl,  
carboxyalkyl or  
alkoxycarbonylalkyl;

35  $R^{10}$  is

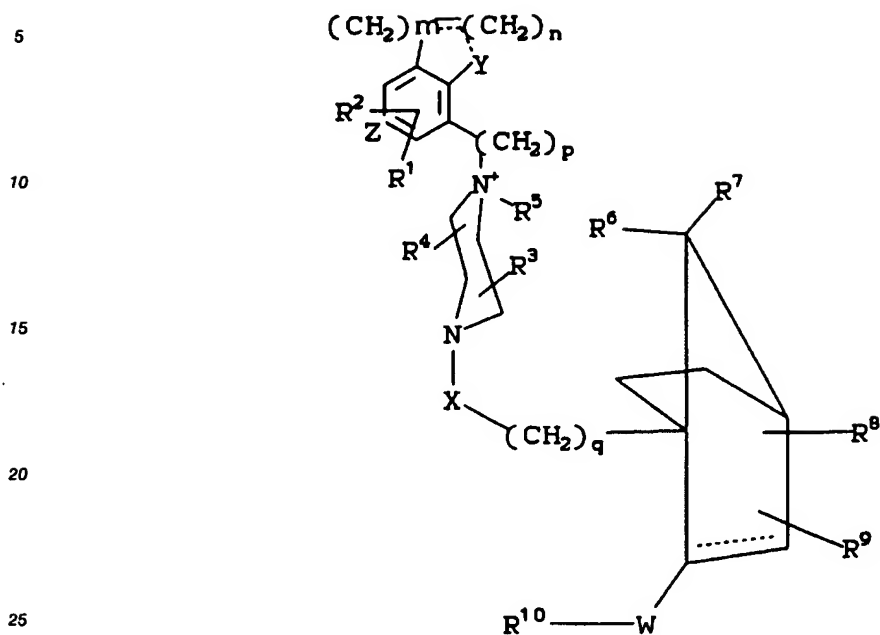
substituted alkyl where said substituent is  $-N(R^{11})-$   
( $R^{12}$ ), where  $R^{11}$  is defined as  
hydrogen or  
40 alkyl, and

$R^{12}$  is defined as

hydrogen or  
substituted or unsubstituted alkyl  
where said substituent is one or more of  
45 (1) hydroxy,  
(2) alkoxy,  
(3) sulfonyl,  
(4) alkylsulfonyl,  
(5) carbonyl,  
50 (6) alkylcarbonyl,  
(7) alkoxycarbonyl,  
(8) carboxy,  
(9) phenyl or,  
(10) unsubstituted 5 or 6-membered unsaturated  
55 heterocyclic rings having one or two heteroatoms  
where in said heteroatom is N; and  
integers from 0 to 2.

$m, n, p$  and  $q$  are

2. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

W is

an optional substituent that, when present, is substituted or unsubstituted alkyl where said substituent is carboxyl;

X is

- (1) carbonyl or
- (2) sulfonyl;

Y is

- (1) hydrogen,
- (2) alkyl or
- (3) NH;

Z is

- (1) C or
- (2) N;

R<sup>1</sup> and R<sup>2</sup> are independently one or more of

- (1) hydrogen,
- (2) halogen,
- (3) alkoxy,
- (4) alkylsulfonyl or
- (5) unsubstituted or substituted alkyl wherein said substituent is;
  - amino
  - alkylamino or
  - dialkylamino;

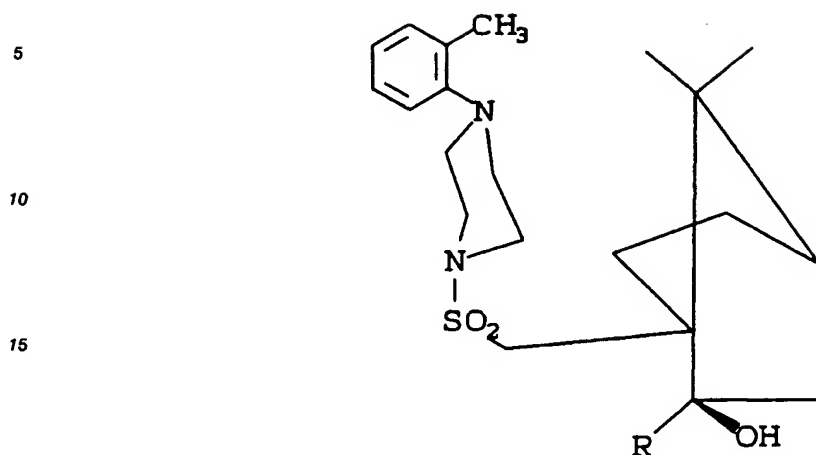
R<sup>3</sup> and R<sup>4</sup> are independently

- (1) hydrogen,
- (2) alkyl,
- (3) substituted alkyl where said substituent is amino

		alkylsulfonyl arylsulfonyl alkylamino dialkylamino;
5		(4) phenylalkyl or (5) oxo;
	R <sup>5</sup> is	(1) hydrogen or (2) oxo;
10	R <sup>6</sup> and R <sup>7</sup> are independently one or more of	(1) hydrogen, (2) alkyl or (3) joined to form unsubstituted or substituted cycloalkyl where said is substituent is
15		hydroxy or hydroxyalkyl;
	R <sup>8</sup> and R <sup>9</sup> are independently one or more of	(1) hydrogen, (2) hydroxy, (3) oxo (4) halogen, (5) oxime, (6) cyclic epoxide, (7) methylene, (8) carboxyl, (9) alkoxycarbonyl, (10) alkylcarbonyloxy, (11) alkoxycarbonylalkoxy, (12) sulfonyloxo, (13) trihaloalkylsulfonyloxo, (14) unsubstituted or substituted amino where said substituent is one or more of
20		alkyl, carboxyalkyl, or alkoxycarbonylalkyl
25		
30		
35	R <sup>10</sup> is	substituted alkyl where said substituent is -N(R <sup>11</sup> )- (R <sup>12</sup> ), where R <sup>11</sup> is defined as
40		hydrogen or alkyl, and
	R <sup>12</sup> is defined as	hydrogen or substituted or unsubstituted alkyl where said substituent is one or more of
45		(1) hydroxy, (2) alkoxy, (3) carboxy, (4) sulfonyl, (5) alkylsulfonyl, (6) alkylcarbonyl, (7) alkoxycarbonyl, (8) aralkoxycarbonyl, (9) phenyl or unsubstituted 5 or 6 member d unsaturated heterocyclic rings having one or two heteroatoms wherein said heteroatom is N; and
50		integers from 0 to 2.
55	m, n, p and q ar	



3. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

R is

substituted alkyl where said substituent is -N(R<sup>1</sup>)(R<sup>2</sup>), where R<sup>1</sup> is defined as hydrogen or alkyl, and

R<sup>2</sup> is defined as

hydrogen or

substituted or unsubstituted alkyl where said substituent is one or more of

(1) hydroxyl,

(2) alkoxy,

(3) carboxy,

(4) alkylsulfonyl,

(5) alkylcarbonyl,

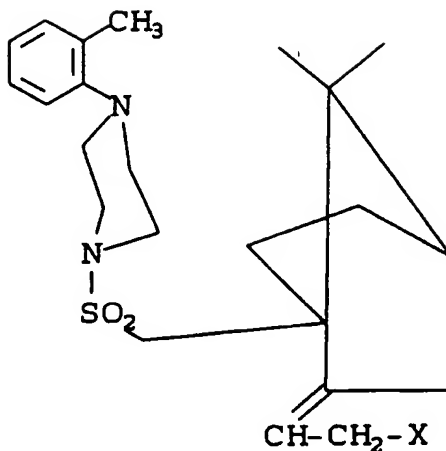
(6) alkoxycarbonyl,

(7) aralkoxycarbonyl,

(8) phenyl or

unsubstituted 5 or 6-membered unsaturated heterocyclic rings having one or two heteroatoms wherein said heteroatom is N.

4. The compound of the formula



and the pharmaceutically acceptable salts thereof, wherein

X is -NR<sup>1</sup>R<sup>2</sup>, -Het or -N<sub>3</sub>;

R<sup>1</sup> is hydrogen or alkyl;

R<sup>2</sup> is hydrogen or unsubstituted or substituted alkyl where said substituent is hydroxyl, carboxyl, alkoxy, alkylsulfonyl, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, phenyl or unsubstituted 5 or 6 member unsaturated heterocyclic rings having 1 or 2 heteroatoms wherein said heteroatom is N;

-Het is unsubstituted or substituted saturated or unsaturated 5 or 6 membered heterocyclic rings containing 1 or 2 heteroatoms where said heteroatom is N and where said substituent is oxo, hydroxy, carboxy or alkyl.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in Claim 1.

6. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for antagonizing the binding of oxytocin to its receptor binding site in a mammalian biologic system.

7. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for preventing preterm labor.

8. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for stopping labor prior to cesarian delivery.

9. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for treating dysmenorrhea.

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number:

**0 533 240 A3**

(12)

**EUROPEAN PATENT APPLICATION**(21) Application number: **92202720.6**(22) Date of filing: **08.09.92**

(51) Int. Cl.<sup>5</sup>: **C07D 295/22, C07D 207/26,  
C07D 233/54, C07D 453/02,  
C07D 303/34, C07D 211/60,  
C07D 207/16, A61K 31/495**

(30) Priority: **16.09.91 US 760271**

(43) Date of publication of application:  
**24.03.93 Bulletin 93/12**

(94) Designated Contracting States:  
**CH DE FR GB IT LI NL**

(98) Date of deferred publication of the search report:  
**29.09.93 Bulletin 93/39**

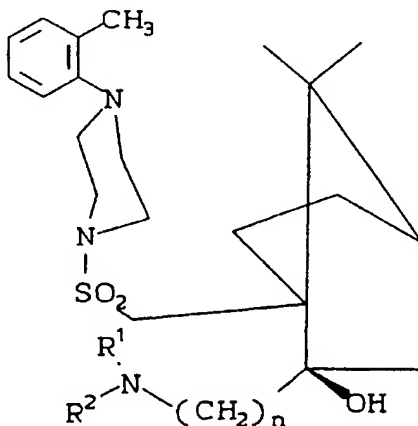
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(54) **Substituted amine derivatives of piperazinylcamphorsulfonyl oxytocin antagonists.**

(57) **Compounds of the formula:**

**I**

The compounds of formula I are oxytocin antagonists useful in the treatment of preterm labor, dysmenorrhea and for the stoppage of labor preparatory to cesarean delivery. Also disclosed are pharmaceutical compositions containing these compounds, methods of their use and methods of their preparation.

**EP 0 533 240 A3**



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 92 20 2720

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-4 147 870 (ANTONIO A. GARCIA) *Document*	1-5	C07D295/22 C07D207/26 C07D233/54 C07D453/02 C07D303/34 C07D211/60 C07D207/16 A61K31/495
A	--- CHEMICAL ABSTRACTS, vol. 86, no. 5, 31 January 1977, Columbus, Ohio, US; abstract no. 29877c, page 376 ;column R ; * abstract * & ES-A-418 775 (LABORATORIOS LIADE S. A.)	1-5	
A	--- FR-A-2 081 346 (LABORATORIOS LIADE S.A.) *Document*	1-5	
A	--- FR-A-2 292 477 (LABORATORIOS LIADE S.A.) *Document*	1-5	
A	--- CHEMICAL ABSTRACTS, vol. 78, no. 5, 5 February 1973, Columbus, Ohio, US; abstract no. 29818u, page 510 ;column L ; * abstract * & ES-A-374 515 (LABORATORIOS LIADE)	1-5	
P,A	--- EP-A-0 486 280 (MERCK) *Document*	1-9	
P,A	--- EP-A-0 450 761 (MERCK) *Document*	1-9	
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The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 12 JULY 1993	Examiner LUYTEN H.W.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	